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Heredity of Fibrosis of the Pancreas

Possible Mutation Rate of the Gene

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INTRODUCTION

REFINEMENTS in diagnosis have made it possible to distinguish the clinical syndrome of fibrosis of the pancreas from other superficially similar diseases. For excellent descriptions of the clinical appearance, diagnosis and pathology of the syndrome the reader is referred to the papers of Andersen (1947) and May and Lowe (1949).

From a genetic point of view this disease appears to be completely lethal since none of the patients has survived long enough to reproduce. Autopsy of the pancreas in adults has never provided unequivocal evidence of the disease. The failure in the past of the patient to survive and transmit his heredity for fibrosis of the pancreas resulted in the loss of genes responsible for the disease each generation. The rather high frequency of the disease in the population indicates that somehow these losses are recouped and presumably the normal and abnormal genes concerned with the disease are approximately in equilibrium.

What has prevented the extinction of the heredity for fibrosis of the pancreas when each patient perishes without progeny? It is proper to assume that some of the genes lost each generation are replaced by the mutation of normal genes in persons without the disease to abnormal genes which express themselves in later generations. It can be accepted without argument that some of the genes which are lost are replaced by the mutation of normal to abnormal genes. Unfortunately, it is not possible to determine whether the replacement of abnormal genes is due largely to mutation or whether there are other important mechanisms which assist in maintaining the genetic equilibrium.

The purpose of this paper is to report the data we have obtained and to weigh the relative importance of the mechanisms which might be responsible for the replacement of the genes lost with the expired patients each generation. It should be kept clearly in mind that while we present a possible mutation rate for the gene causing fibrosis of the pancreas, we have no way of estimating the probability that mutation is, or is not, the most important factor concerned.

Received January 17, 1952.

Our study is an invitation to other workers to contribute data and interpretations to an understanding of mutation rates in man.

Type of Heredity. The earliest suggestion of a definite type of hereditary mechanism was that of Howard (1944) who thought that the disease was produced by a "heterozygous" factor transmitted from one side of the family only. Apparently he thought the disease to be a dominant, the presence of one dose of the deleterious gene being sufficient to produce the condition. If the gene is fully penetrant, the hypothesis of dominance could not be correct, as the gene would become extinct in the generation following mutation and it would be impossible to explain the large numbers of affected relatives observed.

Andersen and Hodges (1946) used genetic techniques to demonstrate clearly that fibrosis of the pancreas appears when a single, simple Mendelian recessive gene is present in the double or homozygous condition. Lowe, May, and Reed (1949) confirmed this conclusion with a different and larger sample of data. In a personal communication, Dr. Cedric Carter, of the London Hospital for Sick Children, states that he has studied the family histories of over 150 cases and his analysis of them gives the same result.

Frequency in Different Racial Groups. Zuelzer and Newton (1949) found that only 3 out of 35 cases of fibrosis of the pancreas were Negroes, and these were probably not "pure" Africans. Thus, only 10% of his cases were colored, though Negroes constitute 35% of the total admissions to the Children's Hospital of Michigan in Detroit.

Personal communications from J. R. Derrick, M.D., at the Charity Hospital at New Orleans and P. D. Trivette, M.D., at the Tulane School of Medicine, New Orleans, revealed no certain case of fibrosis of the pancreas in Negroes, though many were listed for whites. Many definite cases in Negroes should have come to their attention had they existed.

It seems clear that Negroes are afflicted with this disease less often than persons of European descent.

The above is of interest because of the high frequency of sickle cell anemia in Negroes and of thalassemia in Mediterranean countries. Erythroblastosis shows a high frequency among those of European origin and is low among Asiatics. All four of the above diseases demand a high mutation rate, if replacement of the lost gene is primarily by new mutations. All four diseases show sharply different frequencies in different racial groups, with high frequencies in some.

Consanguinity of the Parents. Fibrosis of the pancreas is not a rare disease among families of European origin. Consequently *no* increase of consanguinity among the parents would be expected, nor was any found. Only two cases of consanguineous marriages among the parents of fibrocystic patients have been reported. One instance was observed by Garrod and Hurtley (1913) and the other by Lowe, May, and Reed (1949). The latter found only one first

cousin marriage among the parents of the 118 families studied. This is in agreement with a rate of first cousin marriages of something less than 1% for the U. S. A.

Frequency of the Disease at Autopsy. Andersen and Hodges (1947) report that about 3% of post-mortem examinations at Babies Hospital in New York and at several other hospitals are classified as fibrosis of the pancreas. Harper (1949) reported 3.04% for 755 autopsies at the Royal Alexandria Hospital in Sydney, Australia.

We have obtained, from 19 hospitals throughout the United States, data which indicate that it is correct to utilize 3% as the proportion of hospital deaths coming to autopsy which can be charged to fibrosis of the pancreas.

It should be emphasized that the frequency of a disease at autopsy is *not* equivalent to the frequency of that disease in the general population.

An interesting example of the error which would result from the use of autopsy data as the basis for calculations of the frequency of the disease in the general population may be obtained from the data of Keller and Nute (1949). They reported that of 82,886 admissions of children under 14 years of age to the St. Louis Children's Hospital, 4,669 deaths occurred of which 2,441 were autopsied. Of these post-mortems, 31 cases or 1.27% were diagnosed as juvenile cirrhosis of the liver. Vital statistics of the United States for 1940 record 158,915 deaths of children 14 years of age and younger. Of these, we should expect 1.27%, or 2,018 cases, to have been attributed to juvenile cirrhosis of the liver. However, only 108 deaths were so designated in the same U. S. tables. Thus, 95% of the cases expected to be reported as cirrhosis, on the basis of hospital autopsies, did not materialize. It might be argued that physicians misdiagnose the disease in the majority of cases but this is not a very plausible supposition. It is more reasonable to assume that hospital autopsies represent a biased sample of infant deaths in the whole population. Obviously many accidental deaths of children due to falls, burns, drownings and the like would not have an opportunity to appear in hospital autopsy reports.

Our conclusion is that 3% of cases at autopsy are deaths due to fibrosis of the pancreas, but for a number of reasons, such as the one given above, we cannot use this figure in calculating the frequency of deaths among all infants due to this disease. The result obtained would be too high.

Previous Estimates of the Frequency of the Disease. Andersen and Hodges (1947) used their figure of 3% of autopsy deaths to get a death rate due to fibrosis of the pancreas. In New York State there were 10,804 deaths of children under 14 in 1939. Three per cent of 10,804 is 324 deaths attributed to fibrosis of the pancreas. Dividing 324 by the 187,575 live births in New York State for 1939 gives their published estimate of 1.73 cases of fibrosis per 1000 live births. This value is too high to the extent that autopsy data are unrepresentative of deaths in the whole population. We are indebted to Dorothy Andersen, M.D.,

for sending the above figures to us. We can be certain that the true frequency of the disease is something less than 1.7 cases per 1000 live births, as this figure is definitely the absolute maximum estimate and seems to be higher than actuality.

Lowe, May, and Reed (1949) estimated the range of the frequency for a group of cases at Boston Children's Hospital to be between 1 case per 100 and 1 case per 10,000 live births. Obviously this range is too great to be useful for any precise calculations. Consequently, the range must be narrowed down somewhat before the possible mutation rate of the normal to abnormal gene can be estimated.

The major work of the present paper is the attempt to arrive at a better estimate of the frequency of fibrosis of the pancreas in the general population.

NEW DETERMINATIONS OF THE FREQUENCY OF THE DISEASE

Three sources of information were tapped in order to arrive at a more refined estimate of the frequency of fibrosis of the pancreas. The study was limited to cases receiving attention during the 5-year period from 1945 to 1949 inclusive.

1. Data from "Hospital" Pediatricians. A survey of pediatricians registered as active members of the Society for Pediatric Research or the American Pediatric Society was undertaken to furnish data on the hospital frequency of the disease. In order that no case be reported twice, questionnaires were sent to only one physician at a given office or hospital address. These "hospital" pediatricians were sent an explanatory letter, a reprint of the paper by Lowe, May, and Reed on fibrocystic disease, and a return postcard with the four questions to be answered. These questions follow:

a. Approximately how many hospital admissions of infants and children have come under your care since January 1, 1945?
b. Of these patients, how many had fibrosis of the pancreas?
c. Of all the patients you observed, about how many died? Of these, how many were autopsied?
d. Of those autopsied, about what percentage had fibrosis of the pancreas?

The response to the request for data was satisfactory, 31 out of 60 returned the question card. Since Lowe, May, and Reed (1949) had already presented adequate data for one hospital a comparison of it with that for the whole group should indicate whether the survey technique was valid or not. Table 1 shows that agreement between the two bodies of data is excellent. Consequently we can consider the survey data to be reliable, as a comparison of the two sets of data in a fourfold table gave a X^2 of only 1.08 with a P value between 0.2 and 0.3.

The rate of 1.8 cases of fibrosis of the pancreas per 1000 hospital admissions must be significantly higher than the frequency of the disease in the general

population. This must be so, as a large proportion of children reach the age of 14 years without ever having had a hospital admission.

2. Data from Private Pediatricians. A random sample of approximately 10% of pediatricians in the United States registered with the American Board of Pediatrics was selected. This group was sent an explanatory letter and a return postcard with four requests for data. Since it was anticipated that a 100% response would not be provided, all Minnesota pediatricians registered with the American Board of Pediatrics were surveyed for control purposes. The Minnesota pediatricians who failed to return the data card could be contacted personally and some response obtained from each, thus obtaining a complete sample to compare with the 10% sample for the United States as a whole.

The questions asked of the private practice pediatricians were as follows:

a. Approximately how many newborn infants have come under your care since January 1, 1945?
b. Of these, how many have developed fibrosis of the pancreas?
c. How many of the infants with fibrosis of the pancreas died?

TABLE 1. COMPARISON OF THE DATA FROM LOWE, MAY, AND REED WITH THIS HOSPITAL SURVEY

	LOWE, MAY, AND REED	"HOSPITAL PEDIATRICIANS"	TOTALS
Total Admissions	65,960	237,297	303,257
Cases of Fibrosis of the Pancreas	134	416	550
Rate per 1000 Admissions	2.03	1.75	1.81

d. How many of the patients with fibrosis of the pancreas had siblings or relatives with the disease?

It is gratifying that 46% of all the private pediatricians invited to contribute data, did so. The pediatrician has a busy life and we hesitated to bother him with even four short questions.

It was thought that possibly the practicing pediatricians who responded did so because of having treated a case of the disease, although the introductory letter contained a specific request that they respond whether they had treated a case or not. Half of those responding reported having had *no* cases of fibrosis. It was possible to contact 15 of the 19 Minnesota pediatricians who did not respond to the questionnaire, as a follow-up procedure. Of these 15, we found that 8 had treated at least one case of the disease and 7 had not. There seemed to be no difference between the now "complete" Minnesota group and the small sample (176 responding pediatricians) from the whole registered group in the United States.

The data from the partial sample of United States pediatricians and for the reasonably complete Minnesota sample are given in table 2. The rate is just about one case per 1000 new born infants. This rate is still probably a little

above the actual rate as it probably includes some referrals from non-registered pediatricians, though the explanatory letter asked that referrals *not* be included. Furthermore, many healthy children never see a pediatrician.

There were 241 cases of fibrosis of the pancreas and for 58 of them a relative also was reported to have had the disease. Only 12 physicians volunteered the degree of relationship, 10 reporting a sib with the disease, one a maternal cousin and one a pair of twins both of whom had the disease.

We may conclude that the maximum possible frequency of fibrosis of the pancreas is one case per thousand births, though this rate is probably still higher than actuality.

3. Data from Death Records: We are indebted to Mr. J. W. Brower, Director of the Division of Vital Statistics of the Minnesota Department of Public Health for permission to search the records, and to Miss Gladys Casady and staff for aid in searching.

Death records for the years 1945–1949 are codified according to the 5th Revision of the International Listings of Causes of Death. Because that edition

TABLE 2. DATA FROM PRIVATE PRACTICE PEDIATRICIANS

	UNITED STATES PARTIAL SAMPLE	MINNESOTA "COMPLETE" SAMPLE	TOTALS
Total Newborn Reported Seen	207,323	19,653	226,976
Total Cases of Fibrosis	222	19	241
Rate per 1000	1.1	1.0	1.06
Deaths	94	8	102
Mortality Rate	42%	42%	42%
Number of Affected Relatives	53	5	58

did not list fibrocystic disease as a cause of death, it was necessary to examine *all* the records in code groups in which fibrosis might logically have been placed. Since the oldest case reported in the United States died at 17 years of age (Gibbs, Bostick, and Smith, 1950), the search was limited to deaths of persons 20 years of age or less.

The code groups considered to contain all deaths due to fibrosis of the pancreas were:

107—Bronchopneumonia, including capillary bronchitis.
119—Diarrhea, enteritis and ulceration of the intestine.
122b—Intestinal obstructions.
128—Diseases of the pancreas excluding diabetes mellitus.
157g—Congenital malformations of the digestive tract.
158—Congenital debility.
161a—Asphyxia. Occasionally what is primarily bronchopneumonia is reported as asphyxiation.

From the 1,687 death records pulled according to the classifications above,

there were 23 found to include fibrosis of the pancreas as some part of the medical certification. In addition, 3 records which were selected as probable cases were found to be diagnosed cases of fibrocystic disease when followed up (2 at the University of Minnesota and one at the Mayo Clinic), though the death records themselves did not mention the disease. We consider these 26 deaths to be positive cases of fibrosis of the pancreas. Only 2 of the children were over 5 years of age at death, one 6 and the other 7. These last two were not born in the 1945–1949 period so must be omitted in the following calculations of rate at birth, leaving 24 cases, all of them having been born during the 1945–1949 period.

The total births in Minnesota during 1945–1949 inclusive were 343,604. Of these, 24 were known to have died of the disease. However, these 24 are only a fraction of the total number of cases of fibrosis in the population of births during 1945–1949; the remainder had survived beyond January 1, 1950. Table 2 shows that of the cases known to pediatricians, 42% had died by 1950. Consequently, the 24 reported deaths are only 42% of the total number of cases in the 1945–1949 population of births, and the total number expected including living and dead is 57 children.

We are reasonably certain that of the 343,604 births an absolute minimum of 57 had developed fibrosis of the pancreas during the first five years of life. All 108 cases for which Lowe, May, and Reed had information had shown first symptoms of the disease before they were 16 months old. Consequently, we assume that almost all children with the genotype for the disease, born between 1945–1949, had shown symptoms during that five-year period.

The absolute minimum rate of fibrosis of the pancreas is therefore 343,604 divided by 57, or 0.16 cases per 1,000 births. It would be foolish to consider this low value to be the true rate for the disease. Many cases must have been born and died in rural areas without coming to the attention of a physician familiar with the diagnostic signs. Undoubtedly many cases were certified simply as bronchopneumonia or intestinal obstruction.

Returning to the 1,687 death records pulled to include all possible cases of fibrosis, there were 74 selected as probable cases of the disease. These were selected according to extremely conservative criteria and are only those records where information was unusually detailed. None of these mentioned fibrosis of the pancreas as such but in every case the evidence seemed adequate for a probable diagnosis of fibrosis of the pancreas. There were many sorts of evidence used. For instance, one of the deaths considered "probable" was the younger brother of a girl reported to us by the University Pediatrics Department as a positive case. Yet the boy himself never got to a registered pediatrician.

If we accept the selected 74 "probables" as genuine, we must adjust by the 42% mortality rate which gives a total of 177 "probable" cases. We may then add the 57 positive cases to the 177 probables and get 234 cases. These divided

by 343,604 give a rate of 0.68 per 1000 live births. Even with this addition we must have missed some cases. It would seem reasonable to accept the figure, however, as the minimum possible frequency of the disease, with the expectation that it is lower than the actual rate.

4. Summary of the Frequency Data. The purpose of this experimental work was to narrow the range of frequencies between one case per 100 and one case per 10,000 live births as reported by Lowe, May, and Reed (1949). This was done and the range can now be considered to be from 0.68 cases to one case per 1000 live births. It is assumed that the true rate is somewhere between these rather narrow limits, and probably closer to the upper one of one case per 1000. Rounded off, the range is from 0.7–1.0 per 1000 live births.

CALCULATION OF THE POSSIBLE MUTATION RATE

If the calculation of the mutation rate for any recessive lethal character is ever defensible, it would seem proper to do so for fibrosis of the pancreas. If acceptable, the calculation of the mutation rate is simplicity itself for a recessive lethal. Briefly stated, if the alleles concerned are frequent in the population, and at equilibrium, while the survival and reproductive fitness of the heterozygote is the same as that of the homozygous normal, we find that the mutation rate per chromosome per generation is equivalent to the frequency of lethal children in the population.

Consequently the possible mutation rate for the normal to abnormal gene for fibrosis of the pancreas is between 0.7×10^{-3} and 1.0×10^{-3}. This is a very high mutation rate compared with those which are well established for the lower organisms. Obviously it is suspect because it is at one extreme of the range of mutation which we might expect to find. However, the extreme variants of a series of mutation rates are real and must not be rejected merely because they find themselves among the extreme values. Let us look at the objections to accepting calculations of the mutation rates for recessive lethal characters. These have been clearly stated by Haldane (1948).

The first objection is that the normal and abnormal alleles are not in equilibrium, due to the recent breakdown of isolates. This objection is not so important for a *common* gene such as that for fibrosis of the pancreas, as it would be for a rare gene.

An indication of how frequent the abnormal gene is can be obtained from the estimated frequency of affected individuals. They may be designated as q^2, in the expression $p^2 + 2pq + q^2$, where q is the frequency of the abnormal allele and p the frequency of the normal allele. Using our frequency range for the disease of 0.00068 to 0.001 the values of q are 0.026 to 0.032 and the frequency of the heterozygote, 2pq, is from 0.051 to 0.063. In other words, one person in every 16 to 20 carries the gene for fibrosis of the pancreas, a surprisingly common gene.

A more powerful objection is that the heterozygote might have greater

survival value, reproductive fitness, or both, compared to the normal homozygote. The differential fitness in favor of the heterozygote might account for the maintenance of the defective gene in the population. We have no way of testing what the survival of the heterozygous and homozygous normal genotypes may be. It is possible to speculate as to the productive fitness of the heterozygote as measured by the average number of non-diseased children produced. Using the data of Lowe, May, and Reed (1949), there were 365 children from the heterozygous parents and of them there were 167 with the disease. These 167 were not expected to live long enough to reproduce. This leaves 198 children produced who could be considered as potentially reproductive. These were divided among 110 families for an average of 1.8 children per family who might be expected to reproduce. Obviously, this low average is not enough to maintain the group, though it must be remembered that some of the families were not completed at the time of the study, and that those heterozygotes who produced no abnormal children because of their small family sizes are not available for the study, and cannot be found.

Glass (1950) has suggested that persons having one or more erythroblastotic children compensate for the loss of them by additional pregnancies. It is generally known that in those urban communities where family size is controlled efficiently enough to make compensation necessary, not enough children are produced for replacement. Consequently, groups that intentionally compensate for their losses but at the same time fail to replace themselves could not increase the frequency of the abnormal gene in the population as a whole.

The opinion of C. D. May, M.D., who has worked with fibrosis of the pancreas for many years, is that compensation would not operate extensively and that the prolonged illness and heavy hospital expenses of the sick children would discourage the heterozygous parents from having the normal sized family which they might have planned.

The fact that only a small superiority of the heterozygote in survival, reproductive fitness, or both, would be necessary to replace the lost genes, without resorting to mutation at all, would make studies attempting to measure the difference, if any, between the heterozygote and the normal homozygote unusually difficult. An insoluble problem, at present, is that of detecting those heterozygotes who have not produced an affected child. Without them we cannot estimate the biological effectiveness of the heterozygote compared with the normal homozygote.

In view of the above, experimental attempts to determine the role of mutation in replacing losses of the fibrosis genes would not appear likely to succeed.

DISCUSSION

A marshalling of opinions as to the role of mutation in replacing the loss of genes for fibrosis of the pancreas, via the death of the affected children, will

not prove anything. However, a short discussion might stimulate thinking about mutation rates in man, an important scientific problem.

It was mentioned previously that there are now four human characters known which demand high mutation rates, if mutation is the mechanism by which the gene losses are replaced.

1. Neel (1950) reported that the gene causing sickle cell anemia in Negroes would have to mutate at a rate of 1×10^{-2} chromosomes per generation, a truly staggering figure, as he points out.

2. Next most disturbing, because of its high rate, is the disease, fibrosis of the pancreas, reported here to have a rate of from 0.7 to 1.0×10^{-3}.

3. With erythroblastosis, it is more difficult, though not impossible to allege that the replacement of the lost genes is via the superiority of the heterozygote, because it is the heterozygote that dies of the disease. In this case the prevalent notion is that genetic drift, or some mechanism other than mutation, brought about a high frequency of the rhesus negative genotype in early European tribes, of which the Basques are a present day remnant. We are of the opinion that it would be difficult for genetic drift to bring such a condition about in any appreciable number of people with strong selection, say of 5% deaths among the heterozygotes, against the rhesus negative genotype. Furthermore, the rhesus negative genotype must be fairly high in other regions, such as Africa, because the frequency of the rhesus negative "gene" in American Negroes is about 29.2%. A good proportion of this frequency must have come from Africa as it is not generally considered that American Negroes have more than 50% white genes.

It seems more logical to us that the Basques are the remnants of people showing a high mutation rate to the rhesus negative allele rather than the flotsam of an early European tribe with a rhesus negative gene frequency of over 50%.

What would the mutation rate have to be to replace the rhesus negative genes lost via erythroblastosis?

Haldane (1942) points out that the effect of selection against the rhesus negative "gene" per generation is given by the equation:

$$dp/dt = kp^2(1 - p)(p - \tfrac{1}{2})$$

Where dp/dt is the rate of change in the frequency of the rhesus negative gene, k is the selection against the heterozygote, and p is the frequency of the rhesus negative gene. With p equal to 0.39 for the American white population the expression equals $-0.0102k$. Haldane sets k at 0.05, so that our change in the frequency of the rhesus negative gene each generation would be -0.00051. This is equivalent to the mutation rate per chromosome per generation that would be necessary to replace the losses. The mutation rate would be expressed as 5.1×10^{-4}.

It would seem that the mutation theory of replacement should be given prominent consideration along with the other theories previously elaborated.

4. Neel and Valentine (1947) calculated that if the heterozygote has normal viability, equilibrium would be secured by a mutation rate of 4×10^{-4} from the normal gene to that for thalassemia. They also point out that if the heterozygote had an increased fitness of only 2.1% there would be equilibrium without any mutation at all. Once again we cannot decide between the two major alternatives.

The above four diseases not only agree in that they call for high mutation rates, or superiority of the heterozygote, but also in showing sharp differences in frequency for different racial groups. It would seem that all four are explicable in the same way, whatever the answer may be.

Is it improbable on *a priori* grounds that such high mutation rates exist? Stadler (1948) found a mutation rate in *one* race of *Zea mays* at the R locus of 1.82×10^{-3}. Castle (1951) has collected data from several sources and shown that the average value for mutations at the hooded locus in rats is about 1.4×10^{-4}. It would seem that the human diseases under consideration could well be at this high end of the mutation spectrum.

Reed (1941) showed clearly that Drosophila heterozygous for several different visible "Marker" genes were distinctly inferior in viability, and presumably in reproductive fitness, to the homozygous wild type. Stern and Novitski (1948) showed that a large majority of lethals in the heterozygous condition decrease viability. Even their 2 lethals (out of 33) which seemed to give the heterozygote clearly increased viability were not certain to have had greater reproductive capacity also. There is, indeed, very little precise evidence that the heterozygote for a *particular pair of alleles* is superior to the normal homozygote. It sould seem more reasonable that usually the physiology of the heterozygote is intermediate between the two homozygotes.

The facts are not yet available which would allow a scientific choice between the alternatives of a high mutation rate or the superiority of the heterozygote as the main mechanism of gene replacement involved in the four diseases discussed here. The detection of mutants in the sickle cell anemia project by Neel may answer the question, by inference, for all four diseases. While we are more inclined toward the acceptance of high mutation rates rather than even slight superiority of the heterozygote, there is always room for an entirely distinct and novel explanation of the population genetics of these four most interesting diseases.

SUMMARY

Fibrosis of the pancreas is a simple recessive trait which causes the eventual death of infants and children and genetically speaking, is a lethal. It seems to be fully penetrant.

A comparison and evaluation of data from three sources, hospitals, pediatricians in private practice and death records indicate that the frequency of the disease lies between 0.7 and 1.0 case per 1000 live births. These are the genetic homozygotes all of whom die and with each death the two recessive genes involved are lost from the population. If it is assumed that these lost genes are replaced by mutations from the normal to abnormal allele, the mutation rate per chromosome per generation is equivalent to the frequency of the disease, i.e., 0.7 to 1.0 $\times$ 10^{-3}. This assumes a very high mutation rate, and is suspect because it is so high.

It is pointed out in the discussion that the four highest mutation rates suggested for man, all of which are high enough to invite further study, agree in that they show very high frequencies in other races. It would seem that the answer for all four diseases is the same and the alternative explanations for the replacement of the genes lost via the lethal individuals are either high mutation rates or superiority of the heterozygotes. The present authors are inclined toward the hypothesis of high mutation rates though probably the majority of geneticists would favor superiority of the heterozygote, at least at first glance.

The four diseases are assumed to have mutation rates almost of "ever-sporting" magnitude, and the rates assumed for them, are given below:

Sickle cell anemia	1.0×10^{-2}
Fibrosis of the pancreas	0.7 to 1.0×10^{-3}
Erythroblastosis	5.1×10^{-4}
Thalassemia	4×10^{-4}

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Relative Index Finger Length as a Sex-influenced Trait in Man[1]

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ALTHOUGH a genetic basis has been determined for numerous abnormalities of the hand and foot, relatively little attention has been given to the inheritance of normal variations in shape and structure. One of the most frequently reported normal variations in the human hand is the length of the index finger as compared with the ring finger. Ecker (1875) noted that three manifestations of relative finger length may be discerned in the living model: index finger shorter than ring finger ($2 < 4$); index finger equal in length to ring finger ($2 = 4$); and index finger longer than ring finger ($2 > 4$). Many of the earlier workers failed to recognize this variability in relative index finger length. Gerdy (1829) stated that the index finger is always shorter than the ring finger, while according to Carus (1853) and Humphry (1861), the index finger exceeds the ring finger in length. Langer (1865) declared that the index finger is shorter than or nearly equal to the ring finger. Alix (1867), Grüning (1886), Baker (1888), Schultz (1926), and Wood-Jones (1920, 1941) point out that although the index finger is usually shorter than the ring finger, it may in certain instances exceed the length of the ring finger. Ecker (1875), Mantegazza (1877), Grüning (1886), Baker (1888), Volotzkoy (1924), and Huizinga (1949) each found that all three formulas occur in both sexes but that a relatively long index finger is found more frequently in females than in males. George (1930) studied a Canadian population and found that $2 < 4$ is the most frequent formula in males while a $2 > 4$ formula predominates in females. Volotzkoy (1924), Schultz (1926) and Huizinga (1949) have noted that the various formulas may also be observed in fetuses.

Although Kloepfer (1946) has suggested that the variations in relative index finger length may be hereditary, no attempt has been made to establish

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the genetic basis for these formulas. The present investigation was undertaken to determine the mode of inheritance for relative index finger length and, insofar as possible, how the genes act to produce such variations. Study of the inheritance of normal traits, which have a high incidence and which develop early in fetal life, makes possible a more fundamental understanding of what rôles the genes may play in normal growth and development.

Since relative index finger length is considered to be a "normal" trait in that it is not associated with any type of abnormality, and since the variations in index finger length occur with a high incidence in the population, this trait should be particularly useful in linkage studies. If the gene which determines relative index finger length can be shown to be closely linked genetically with a gene for a severe disease having late onset or low penetrance, then this information may be valuable as a diagnostic aid.

MATERIALS AND METHODS FOR GENETIC ANALYSES

The material for population analysis consisted of outline drawings of the hands, collected at random, from students and faculty members of the Biological Laboratories of The University of Texas. Data regarding age, sex, height, religion, and nationality background were obtained from each person. The series consisted of 284 persons, of whom 189 were males and 95 were females, and was comprised of individuals belonging to the White race. For familial analysis, drawings were obtained from members of 20 families, containing 26 sibships taken from families of student and faculty members of The University of Texas and residents of Minneapolis, Minnesota.

Measurements of the relative lengths of the index and ring fingers were made from outline drawings of the left hand by using the pivot-ruler method (a new method developed by the author). In this method the left hand is placed flat on a sheet of heavy paper, so that the middle finger is in line with the arm. A thin, sharply pointed pencil is used to trace around the hand, special care being taken around the tips of the fingers and at the angles between the fingers. A celluloid ruler, 5 cm. wide, with a metric scale along each edge and having a small hole on the 0 mm. line, 2 cm. to the left of the right scale, is placed on the outline drawing of the hand so that the hole is directly over the most proximal point of the angle between the index and middle fingers. The ruler is pivoted, on a pin inserted through the hole, until the right metric scale is in line with the axis of the index finger; a reading is recorded for the length of the index finger. The ruler is again pivoted, until the left scale is parallel to the axis of the ring finger; the corresponding length of the ring finger is recorded. The length of the ring finger is subtracted from that of the index finger to determine the difference in the relative lengths of the two fingers.

Measurements of the relative lengths of the index and ring fingers were also made directly from the hands by using a hand-measuring board, similar in

construction to that devised by George (1930), to permit comparison of the present population with the Canadian population studied by George (1930). The relative index finger length for any one individual was found to be the same when both the pivot-ruler and hand-measuring board methods were used.

The hands were classified into three groups: index finger shorter than ring finger, $2 < 4$; index finger equal in length to ring finger, $2 = 4$; and index

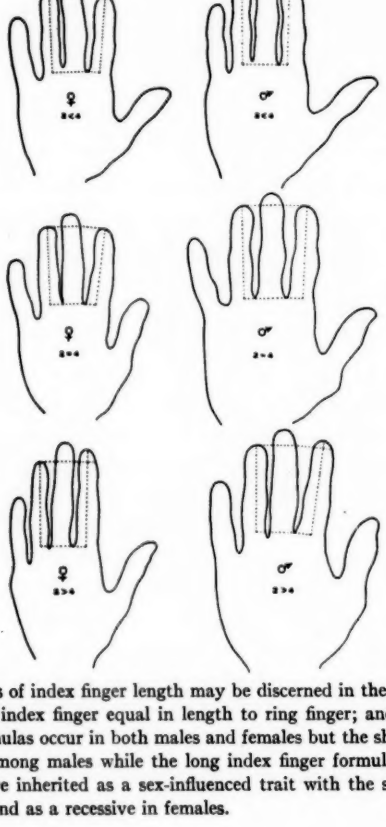

FIG. 1. Three formulas of index finger length may be discerned in the human hand: index finger shorter than ring finger; index finger equal in length to ring finger; and index finger longer than ring finger. All three formulas occur in both males and females but the short index finger formula is the most frequent one among males while the long index finger formula predominates among females. These formulas are inherited as a sex-influenced trait with the short index formula acting as a dominant in males and as a recessive in females.

finger longer than ring finger, $2 > 4$, fig. 1. At first the index and ring fingers were considered to be equal in length if the difference in the relative lengths of the two fingers was 2 mm. or less, since a difference of this magnitude was apparent by observation of either the hand or the outline drawings, and did not require the use of special measuring devices. The use of a pivot-ruler, however, made possible more accurate determination of relative index finger

length. The hands were then reclassified by using a more critical value for index finger length determination, wherein the index and ring fingers were considered equal in length *only* if the recorded difference in the relative lengths of these two fingers was less than 1 mm. The formula found on the left hand was used for classification purposes in both population and family history analyses, since the right and left hands of an individual usually showed the same formula, and since use of the left hand is standard anthropological procedure.

Two types of genetic analyses of relative index finger length were employed: (1) population analysis, and (2) familial analysis. The populations were analysed for the frequency of the various formulas in males as compared with females, and for the mode of inheritance by the mass method as developed by Snyder and Yingling (1935). The observed frequency of the formulas in the population varied with the two values (2 mm. or less than 1 mm. for $2 = 4$) used for formula determination; therefore each resulting distribution of frequencies was analysed separately by the mass method. The Canadian population reported by George (1930) was also analysed by the mass method for comparison with the present population.

Each of the family histories collected for the present study, and most of the sibships used by Kloepfer (1946) in his linkage analysis, were studied individually to see if the histories agreed with the mode of inheritance determined by the mass method gene frequency analysis. All of the histories were analysed, according to mating type, for the expected proportions of homozygous individuals among the offspring following the method devised by Phelps (1948). Only the more critical value (less than 1 mm.) was used for determining the formulas of the members of the family histories in the present study. Since in Kloepfer's data all individuals having a $2 = 4$ formula were grouped with those showing different formulas on right and left hands, not all of the histories from his data could be utilized.

POPULATION ANALYSIS

When the population used in the present study is classified according to the relative length of the index finger, all three formulas ($2 < 4$, $2 = 4$, and $2 > 4$) are found to be present in both males and females, fig. 1. The frequency distribution of the formulas differs, however, within the two sexes, and also shows some variation depending upon the value used for formula determination.

If the index and ring fingers are classified as being equal in length when their difference in relative projection is no greater than 2 mm., it may be seen in table 1 that a relatively short index finger occurs with a higher frequency in males than in females, while a longer index finger is found more commonly in females. Since a difference of 2 mm. is discernible to the unaided eye, it is probable that a value of approximately this magnitude was used by those

workers who made classifications without the aid of measuring devices. The data from this population agrees with the findings of Ecker (1875) and Grüning (1886), and also, in general, with those of Volotzkoy (1924) and Huizinga (1949)

The use of the more critical value for determination of index finger length formulas, wherein the index and ring fingers are considered to be of equal length if the difference in their relative projection is *less* than 1 mm., results in an even greater diversity in the frequency distribution in the two sexes than is obtained using the 2 mm. value (table 1). A short index finger not only occurs more commonly in males than in females but actually constitutes the predominating class in males. The females show the reverse of this situation in that the long index finger class predominates over the other two classes.

These findings are in agreement with the data reported by George (1930) from a Canadian population. In his investigation, George considered the index and ring fingers to be equal in length if the difference in their relative projection was 0.5 mm. or less, as measured by a hand-measuring board. The frequencies which George found are very similar to those obtained in the present study with the use of a less than 1 mm. value (table 1). When the two sets of data are

TABLE 1. FREQUENCY DISTRIBUTION OF FORMULAS IN PERCENTAGES

SEX	PRESENT STUDY						GEORGE, 1930		
	2.0 mm.			< 1.0 mm.			0.5 mm.		
	2 < 4	2 = 4	2 > 4	2 < 4	2 = 4	2 > 4	2 < 4	2 = 4	2 > 4
Males	43.4	40.7	15.9	59.2	13.8	27.0	65	15	20
Females	25.3	37.9	36.8	30.5	12.6	56.8	28	25	47

analysed with respect to the proportions of females showing a short index finger and the proportions of males with a long index finger, it is found that the deviation is 0.025 ± 0.064 in the case of females, and 0.07 ± 0.043 in the case of males. The two populations, therefore, do not differ significantly from one another, and apparently values of 0.5 mm. or less (George, 1930) and less than 1 mm. (present study) serve equally well for determining the formulas.

The observed associations of a short index finger with the male sex and a long index finger with the female sex in the data presented here, as well as in the data of Ecker (1875), Mantegazza (1877), Grüning (1886), Volotzkoy (1924), George (1930), and Huizinga (1949), show that the sex of the individual plays a rôle in determining the formula of relative index finger length. Such associations further suggest that the difference in distribution of formula frequencies in males as compared with females may be due to a sex-influenced mode of inheritance.

If relative index finger length is postulated to be a sex-influenced trait, inherited in the same manner as is baldness (Snyder, 1934), letting I^s represent the gene for a relatively short index finger, and I^L represent the gene for a

relatively long index finger, the corresponding genotypes and phenotypes should be as follows:

Males	Females
I^SI^S = short index	I^SI^S = short index
I^SI^L = equal or short index	I^SI^L = equal or long index
I^LI^L = long index	I^LI^L = long index

An analysis for sex-influenced inheritance of a trait can be made directly from the population known for that trait. If the trait is sex-influenced, it is possible to identify individuals who are homozygous for either of the alleles concerned and thus to derive the respective gene frequencies. Using the mass method of gene frequency analysis for a sex-influenced trait, reported by Snyder and Yingling (1935), p represents the frequency of gene I^s in a given population and q represents the frequency of its allele I^L. Since the phenotypes in heterozygous males and females differ, the sex of the offspring produced by

TABLE 2. DISTRIBUTION OF GENOTYPES IN A RANDOM BREEDING POPULATION

MALES / FEMALES	$\frac{p}{2}$ I^SX	$\frac{p}{2}$ I^SY	$\frac{q}{2}$ I^LX	$\frac{q}{2}$ I^LY
p I^SX	$\frac{p^2}{2}$ I^SI^SXX	$\frac{p^2}{2}$ I^SI^SXY	$\frac{pq}{2}$ I^SI^LXX	$\frac{pq}{2}$ I^SI^LXY
q I^LX	$\frac{pq}{2}$ I^SI^LXX	$\frac{pq}{2}$ I^SI^LXY	$\frac{q^2}{2}$ I^LI^LXX	$\frac{q^2}{2}$ I^LI^LXY

The symbol p represents the frequency of gene I^S and q, the frequency of gene I^L. (Based on Snyder and Yingling, 1935.)

a random breeding population must be considered. For this purpose the X and Y chromosomes may be used in conjunction with the alleles for the trait as shown in table 2.

It can be seen in table 2 that the frequency of females with a short index finger, $2 < 4$, can be represented as $\frac{p^2}{2}$, which constitutes one-half of all I^SI^S individuals. Likewise the frequency of males with a long index finger, $2 > 4$, in a population can be denoted as $\frac{q^2}{2}$.

Then:

$\frac{p^2}{2}$ = proportion of $2 < 4$ females in a total population

$\frac{q^2}{2}$ = proportion of $2 > 4$ males in a total population

Then let:

$\overline{♀ I^S I^S}$ = proportion of 2 < 4 females among females

$\overline{♂ I^L I^L}$ = proportion of 2 > 4 males among males

Assuming that one-half of the population will be females and one-half will be males:

$$\frac{p^2}{2} = \frac{\overline{♀ I^S I^S}}{2} \qquad p = \sqrt{\overline{♀ I^S I^S}}$$

$$\frac{q^2}{2} = \frac{\overline{♂ I^L I^L}}{2} \qquad q = \sqrt{\overline{♂ I^L I^L}}$$

Since $p + q = 1$, then $\sqrt{\overline{♀ I^S I^S}} + \sqrt{\overline{♂ I^L I^L}}$ should equal unity, if relative index finger length is sex-influenced in its mode of inheritance. The two sets of formula frequencies derived from the population in this study and the frequencies obtained from the population studied by George (1930) give the values shown in table 3 for p and q, the deviations of their sums from unity, and the standard error of each deviation.

TABLE 3. GENE FREQUENCY ANALYSIS BY THE MASS METHOD OF SNYDER AND YINGLING (1935)

VALUE FOR FORMULA DETERMINATION	DERIVED p	DERIVED q	DEVIATION FROM UNITY	DEV. / S.E.
2.0 mm.	0.503	0.399	0.098 ± .055	1.78
1.0 mm.	0.550	0.520	0.070 ± .053	1.32
0.5 mm.	0.529	0.447	0.024 ± .057	.425
(George, 1930)				

The standard error was computed from the following formula (Snyder and Yingling, 1935):

$$\text{S.E.} = \pm \frac{1}{2} \sqrt{\frac{1 - B}{N_1} - \frac{(1 - B)^2}{16B(N_1)^2} + \frac{1 - D}{N_2} - \frac{(1 - D)^2}{16D(N_2)^2}}$$

where $B = \sqrt{\overline{♀ I^S I^S}}$, $D = \sqrt{\overline{♂ I^L I^L}}$, N_1 = number of individuals from which B was derived, and N_2 = number of individuals from which D was derived.

Since the deviations obtained from the summation of each set of p and q values are in each case less than two times the standard error, the theory of sex-influenced inheritance for relative index finger length is substantiated. It should be noted that the more critical the value used for formula determination, the closer the sum of p plus q approaches unity.

FAMILIAL ANALYSIS

Analysis of the sibships collected for the present study and those reported by Kloepfer (1946) shows that 41 of the 43 sibships thus far investigated ex-

hibit phenotypic relationships between parents and offspring that are in complete agreement with the theory of sex-influenced inheritance. As may be seen in table 4, four mating types are possible with regard to the formulas found in the parents (omitting the 2 = 4 formula), and the types of offspring possible from such matings are shown in the right hand column. For purposes of computation, the heterozygous condition, even if recognizable by the presence of a 2 = 4 formula, is grouped with the respective dominants in each sex. Thus a 2 = 4 male is placed with 2 < 4 males and a 2 = 4 female is placed with

TABLE 4. PHENOTYPIC RELATIONSHIPS BETWEEN PARENTS AND OFFSPRING*

TYPE OF MATING	GENOTYPES OF MATINGS	OFFSPRING
2 > 4♂ × 2 < 4♀	I^LI^L♂ × I^SI^S♀	♂ = all 2 < 4 ♀ = all 2 > 4
2 > 4♂ × 2 > 4♀	I^LI^L♂ × I^LI^S♀	♂ = ½ 2 < 4, ½ 2 > 4 ♀ = all 2 > 4
	I^LI^L♂ × I^LI^L♀	♂ = all 2 > 4 ♀ = all 2 > 4
2 < 4♂ × 2 < 4♀	I^LI^S♂ × I^SI^S♀	♂ = all 2 < 4 ♀ = ½ 2 < 4, ½ 2 > 4
	I^SI^S♂ × I^SI^S♀	♂ = all 2 < 4 ♀ = all 2 < 4
2 < 4♂ × 2 > 4♀	I^LI^S♂ × I^LI^S♀	♂ = ¾ 2 < 4, ¼ 2 > 4 ♀ = ¼ 2 < 4, ¾ 2 > 4
	I^LI^S♂ × I^LI^L♀	♂ = ½ 2 < 4, ½ 2 > 4 ♀ = all 2 > 4
	I^SI^S♂ × I^LI^S♀	♂ = all 2 < 4 ♀ = ½ 2 < 4, ½ 2 > 4
	I^SI^S♂ × I^LI^L♀	♂ = all 2 < 4 ♀ = all 2 > 4

* For purposes of computation, the heterozygous condition, even if recognizable by the presence of a 2 = 4 formula, is grouped with the respective dominants in each sex.

2 > 4 females. Investigation of sibships, wherein the parental phenotypes are known, makes possible a confirmation of the results obtained from population studies.

Of the four possible mating types, 2 > 4♂ × 2 < 4♀ has been observed in only three instances. Based upon the calculated gene frequencies, this mating type has the lowest probable frequency of occurrence, 0.08, which explains its rarity. Since this mating type was of necessity, according to the theory, one of I^LI^L♂ × I^sI^s♀, the resulting offspring should all have been heterozygous

and there should have been no 2 > 4 males or 2 < 4 females produced. Two of the three histories agree with the expected types of offspring, but one history shows an only child, a daughter, with a 2 < 4 formula which is inconsistent with the theory of sex-influenced inheritance.

Matings of 2 > 4♂ × 2 > 4♀ are expected to occur with a frequency of 0.21, and 8 sibships from such matings have been collected. The father with a 2 > 4 formula must be homozygous I^LI^L and therefore, none of the daughters is expected to show a 2 < 4 formula. The sons may show any of the three formulas depending upon the genotype of the mother. The offspring of 7 of the 8 matings exhibit phenotypes which are in agreement with the theory of inheritance; however, one sibship consisting of 2 females, both of whom show a 2 < 4 formula, is at variance with the expected results.

Matings between 2 < 4♂ and 2 < 4♀ have a probable frequency of occurrence of 0.24 and 18 sibships from such matings have been recorded. The mother must be homozygous I^sI^s to appear phenotypically 2 < 4; therefore, all of the sons from such a mating should have a 2 < 4 or 2 = 4 formula. The daughters may be 2 < 4 or show either of the other two formulas depending upon whether the father is heterozygous or homozygous for the I^s gene. The absence of 2 > 4 males among the offspring is in conformity with the theory of sex-influenced inheritance. Females showing a 2 > 4 formula occurred in 6 of the sibships, indicating that in these sibships at least, the father must have been heterozygous.

The combination 2 < 4♂ and 2 > 4♀ is the only mating wherein all four (or six, if the heterozygous condition is expressed as 2 = 4) classes of offspring are expected to occur, and only then if both parents are heterozygous. Out of 14 such matings, only one showed all four classes of offspring. In 7 of the matings at least one offspring was a 2 > 4♂ or a 2 < 4♀ indicating that at least one of the parents was heterozygous.

Traits that are sex-influenced in their mode of inheritance differ from other autosomal traits not only with regard to the possible types of offspring which may be produced by a particular mating, but also with regard to the frequencies with which such offspring are produced. Therefore, another method of familial analysis has been used wherein the expected proportions of homozygous individuals are compared with the observed proportions resulting from a given mating type, following the method of Phelps (1948). The equations for expected proportions of homozygous individuals, i.e. 2 > 4♂ (I^LI^L) and 2 < 4♀ (I^sI^s), are derived by multiplying the product of the parental genotype frequencies (shown in table 5) by $\frac{1}{2}$ (the chance for producing a male or female) and multiplying this product in turn by the chances for producing the desired type of offspring.

Matings between 2 > 4♂ and 2 < 4♀ occurred in 3 instances producing 5

offspring (table 6). Since in this case all of the offspring are alike genetically, it is not possible to analyse for phenotypic proportions.

Matings between $2 > 4$♂ and $2 > 4$♀ occurred in 8 instances producing 12 offspring (table 6). The matings in this group may have been either I^LI^L♂ × I^LI^L♀, or I^LI^L♂ × I^SI^L♀. From such matings $2 < 4$ males can be produced only if the mother is heterozygous. The expected proportion of $2 < 4$ males can be calculated, and the expected proportion of $2 > 4$ males can be derived as the difference of the proportion of $2 < 4$ males from unity. The equation for the proportion of $2 < 4$ males is shown by the following:

$$\frac{q^2}{q^2} \times \frac{2pq}{2pq + q^2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1 - p}{4 - 2q}$$

TABLE 5. GENOTYPE FREQUENCIES OF MALES AMONG MALES AND FEMALES AMONG FEMALES AS PROPORTIONS OF THE PHENOTYPES RECOGNIZABLE WITHIN THE RESPECTIVE SEX IN A RANDOM BREEDING POPULATION

GENOTYPE	FREQUENCY OF ♀ AMONG ♀	FREQUENCY OF ♂ AMONG ♂
I^SI^S	$\frac{p^2}{p^2}$	$\frac{p^2}{p^2 + 2pq}$
I^SI^L	$\frac{2pq}{2pq + q^2}$	$\frac{2pq}{p^2 + 2pq}$
I^LI^L	$\frac{q^2}{2pq + q^2}$	$\frac{q^2}{q^2}$

The proportion of $2 > 4$ males is derived as:

$$1 - \frac{1 - q}{4 - 2q} = \text{expected proportion of } 2 > 4 \text{ males}$$

The value of q which was calculated in the population analysis is substituted into the above formula. The expected proportion of $2 > 4$ males is found to be 0.838 and that of $2 < 4$ males, 0.162. Referring to table 6, it may be seen that the deviation between the expected and observed proportions is only on the borderline of significance; therefore the theory of sex-influenced inheritance is not invalidated. The occurrence of two $2 < 4$ females is, however, unexpected.

Matings between $2 < 4$♂ and $2 < 4$♀ occurred in 18 instances producing 135 offspring (table 6). The matings belonging to this group may be I^SI^S♂ × I^SI^S♀ and I^SI^L♂ × I^SI^S♀. Referring to table 4 it can be seen that $2 > 4$ female offspring are possible only from matings in which the father is heterozygous. If the expected frequency of $2 > 4$ females is calculated, then the expected frequency of $2 < 4$ females will be 1 minus the expected frequency of $2 > 4$ females. The equation for the expected frequency of $2 > 4$ females is

based on the probability of a heterozygous male, I^sI^L, mated to a homozygous female, I^sI^s, and is shown by the following:

$$\frac{2pq}{p^2 + 2pq} \times \frac{p^2}{p^2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1 - p}{4 - 2p}$$

The frequency of $2 < 4$ females is derived as:

$$1 - \frac{1 - p}{4 - 2p} = \text{expected proportion of } 2 < 4 \text{ females}$$

The value of p, as derived from the population analysis, when substituted into the formula gives an expected proportion of 0.155 for $2 > 4$ females and 0.845 for $2 < 4$ females. Since the deviation between the expected and observed proportions of $2 < 4$ females is not significant (table 6), the observed proportion of $2 < 4$ females fits the theory of sex-influenced inheritance. Also, the absence of $2 > 4$ males in the offspring of this mating type gives further support to the theory.

Matings between $2 < 4$ males and $2 > 4$ females occurred in 14 instances producing 50 offspring in the ratios shown in table 6. The expected frequency of $2 < 4$ females from such matings is derived as the sum of frequencies from each genetic mating type wherein it is possible to produce such offspring. In the case of an $I^sI^L\male \times I^sI^L\female$ mating, the expected frequency of $2 < 4$ is calculated as:

$$\frac{2pq}{p^2 + 2pq} \times \frac{2pq}{2pq + q^2} \times \frac{1}{2} \times \frac{1}{4} = \frac{p - p^2}{4 + 2p - 2p^2}$$

When the value of p is substituted into the formula, a value of 0.055 is obtained as the expected frequency of $2 < 4$ females. In a like manner, the frequency of $2 < 4$ females from an $I^sI^s\male \times I^sI^L\female$ mating can be calculated as:

$$\frac{p^2}{p^2 + 2pq} \times \frac{2pq}{2pq + q^2} \times \frac{1}{2} \times \frac{1}{2} = \frac{p^2}{4 + 2p - 2p^2}$$

resulting in a value of 0.067 as the expected frequency of $2 < 4$ females. The two frequencies are summed, showing that the total frequency for $2 < 4$ females from matings of $2 < 4\male \times 2 > 4\female$ is expected to be 0.122, and the frequency for $2 > 4$ females is 0.878. When the expected and actual frequencies are compared, the results shown in table 6 are obtained. The deviation from the expected is not significant thereby substantiating the theory of inheritance.

The expected frequency of $2 > 4$ males is calculated as the sum of the frequencies from matings of $I^sI^L\male \times I^sI^L\female$ and $I^sI^L\male \times I^LI^L\female$. In the former case, the equation used is:

$$\frac{2pq}{p^2 + 2pq} \times \frac{2pq}{2pq + q^2} \times \frac{1}{2} \times \frac{1}{4} = \frac{q - q^2}{4 + 2q - 2q^2}$$

Substituting for q, the expected frequency of 2 > 4 males from such matings is 0.055. In the latter type of mating the frequency of 2 > 4 males is derived from the following equation:

$$\frac{2pq}{p^2 + 2pq} \times \frac{q^2}{2pq + q^2} \times \frac{1}{2} \times \frac{1}{2} = \frac{q^2}{4 + 2q - 2q^2}$$

TABLE 6. ANALYSIS OF FAMILY HISTORIES FOR EXPECTED PROPORTIONS OF HOMOZYGOTES

MATING TYPE	OFFSPRING FORMULAS	OBSERVED NUMBER	OBSERVED PROPORTION	EXPECTED PROPORTION	DEVIATION	DEV./S.E.
2 > 4♂ × 2 < 4♀	2 < 4♂	3	1.000	1.000	.000	
3 sibships	2 > 4♂	0	0.000	0.000		
5 sibs	2 < 4♀	1	0.500	0.000	.500	
	2 > 4♀	1	0.500	1.000		
2 > 4♂ × 2 > 4♀	2 < 4♂	3	0.429	0.162	.367 ± .150	2.44
8 sibships	2 > 4♂	4	0.471	0.838		
12 sibs	2 < 4♀	2	0.400	0.000	.400	
	2 > 4♀	3	0.600	1.000		
2 < 4♂ × 2 < 4♀	2 < 4♂	60	1.000	1.000	.000	
18 sibships	2 > 4♂	0	0.000	0.000		
135 sibs	2 < 4♀	67	0.893	0.845	.048 ± .042	1.14
	2 > 4♀	8	0.107	0.155		
2 < 4♂ × 2 > 4♀	2 < 4♂	27	0.771	0.885	.114 ± .055	2.07
14 sibships	2 > 4♂	8	0.229	0.115		
50 sibs	2 < 4♀	4	0.286	0.122	.164 ± .091	1.81
	2 > 4♀	11	0.714	0.878		

which, when substituted for q, gives a value of 0.060 as the expected frequency for 2 > 4 males. The two frequencies are summed giving an expected frequency of 0.115 for 2 > 4 males; the frequency for 2 < 4 males is 0.885. Comparing the observed and expected frequencies, the results shown in table 6 are obtained. Since the deviation from the expected is not a significant one, the theory of sex-influenced inheritance is given support.

From the results obtained in the familial analysis, it is seen that the observed parental and offspring phenotypes are in agreement with the expected types in all but two of the histories thus far investigated. Mutation may be consid-

ered as a possible explanation for these two exceptional histories. The observed frequencies with which the phenotypes occur in the offspring do not show significant deviations from those expected. The postulation, based on population analysis, that relative index finger length is inherited as a sex-influenced trait is therefore corroborated by the analysis of the family histories.

ANATOMICAL BASIS FOR VARIABILITY IN FORMULAS

The determination that the formulas of relative index finger length are an inherited characteristic and that this trait appears to have a sex-influenced mode of inheritance, does not in itself explain which elements in the hand are responsible for the observed variations in index finger length, nor in what manner they contribute to this variability. The question arises as to whether the observed formulas are the results of differences in the relative length of the index and ring digits (sum of the three phalanges), differences in the relative length of the index and ring metacarpals, or differences in relative ray lengths (sum of metacarpal and digit lengths). General body build must also be considered as a possible factor in the determination of index finger length formulas.

Ecker (1875) and Grüning (1886) have referred to the high degree of association which they believe exists between a long index finger and an over-average height. The present study shows, on the contrary, a lack of significant association between the various formulas of relative index finger length and the height of the individual, the probability of random assortment being 0.80–0.90 in males and 0.20–0.30 in females. Thus it appears that the formulas of index finger length are not determined by overall growth factors and must instead find their basis in factors which act directly on elements of the hand.

In a morphological study of bone length in the hand, Pfitzner (1892) found that the absolute length of the ring digit always exceeds that of the index digit to some degree. The ring ray, however, may be longer than, shorter than, or equal in length to the index ray. Therefore, he concluded that the relative length of the index and ring rays, rather than the relative length of the digits, determines the formula of index finger length. Such a theory, however, is not tenable in the light of the present study, since an analysis of his data shows that no difference exists with respect to the frequency of males or females having index rays shorter than or longer than the ring rays. Such a difference would necessarily be present if ray length is the basis for this sex-influenced trait.

Wood-Jones (1920, 1941) has postulated that a relatively long index finger may be due solely to an increase in the relative length of the index digit irrespective of the length of the metacarpal. As evidence for this theory, he cites the fact that a hand having a formula of $2 > 4$ may have an index metacarpal which is equal in projection to the ring metacarpal, while conversely, a hand showing $2 < 4$ may have an index metacarpal which projects longer than the

ring metacarpal. Comparison of digit and metacarpal lengths in the data of Pfitzner (1892) supports the observation of Wood-Jones. The difference in index and ring digit lengths ($d_2 - d_4$) and the difference in index and ring metacarpal lengths ($m_2 - m_4$) assort at random in both males and females, the correlation coefficients being $-.115$ and $-.005$ respectively. Therefore, the index finger length formula is not a reflection of metacarpal length, but rather, constitutes an independent characteristic of the hand.

The basis for the variations in formula seems to lie, therefore, in the relationship between the index and ring digit lengths. It is necessary, however, to ascertain whether both the index and ring digits vary with respect to the rest of the hand, or whether, as Wood-Jones (1920, 1941) has suggested, the index digit varies independently of all other elements in the hand. Calculation of the mean ratios between index, middle, and ring digit lengths from the data of Pfitzner (1892) shows that the mean ratio of the length of the middle digit to the length of the ring digit is approximately the same in males and females. The mean ratios of the length of the ring digit to the index digit, and the length of the middle digit to the index digit are, however, greater in males than in females (table 7). These results indicate that the index digit is relatively shorter

TABLE 7. MEAN RATIOS OF DIGIT LENGTHS CALCULATED FROM DATA OF PFITZNER (1892)

	3/4	3/2	4/2
Males	103.85	113.17	109.01
Females	103.99	112.59	108.29

in the majority of males as compared to females, while the relative length of the ring digit is not so influenced by the sex of the individual.

BASIS FOR THE SEX DIFFERENCE IN FORMULA FREQUENCY

The postulation of sex-influenced inheritance as the mode of transmission for relative index finger length necessarily presupposes that the sex of the individual is responsible for the differences in formula which are expressed in heterozygous males and females. Although in some cases the heterozygous individuals, either male or female, are recognizable by the presence of a $2 = 4$ formula, in the majority of heterozygotes either gene I^s or I^L is sufficiently dominant so that a $2 > 4$ formula is expressed in heterozygous females and a $2 < 4$ formula in heterozygous males.

The shift in phenotype which occurs in the heterozygous condition in sex-influenced traits has been variously explained on the basis of hormones or the activity of modifying genes on the X-chromosome. In either case, the balance between the sex factors and the genes responsible for the sex-influenced trait determines the phenotypic expression of the trait. However, the necessity of hormone for gene expression requires that the trait cannot be manifest until

such time as hormone production has been initiated. The age of onset for a sex-influenced trait (pre-natal, pre-puberty, or post-puberty) may therefore suggest which type of factor might be responsible for the sex differences in the phenotypic expression in the heterozygous condition.

Two divergent views have been expressed not only with regard to the earliest appearance of the three formulas of index finger length, but also as to the stability of these formulas during growth and development. Schultz (1926) found that differences in index finger length formula could be observed in the third month of fetal life and in all age groups thereafter. He suggested that the formation of a long index finger is progressive, because he found its occurrence was *rare* in the earliest fetuses but approached the frequency found in adults towards the end of fetal life. He believed that there was little if any change in the formula of an individual after birth. Huizinga (1949), on the other hand, reported that *all* fetuses under four months of age have a long index finger formula. Furthermore, he stated that the frequency of $2 > 4$ types decreases during the later fetal period, and continues to do so until maturity, the decrease being less marked in females than in males.

In the present study, preliminary investigations disclose that all three formulas of index finger length may be discerned as early as the end of the seventh week of fetal life, at which time the terminal phalanges have just differentiated as areas of condensed tissue from the mesenchyme. A sufficient number of fetuses has not as yet been studied to determine the relative frequency of the formulas in various age groups and with respect to sex. It is definitely established, however, that at no time after seven weeks is any one of the formulas absent. The question of stability of the formula in the post-natal period needs to be further investigated by formula determinations on the same individuals over a period of years. The fact that the offspring from the family histories presented in this study agree in formula with those expected on the basis of the genetic theory (with but two exceptions), strongly suggests that the formulas are stable after birth.

At the end of the seventh week when the formulas are first observable, the fetal gonads are just in the process of sex differentiation presumably under the influence of the genic balance between the autosomes and the X-chromosomes, rather than hormones (Moore, 1948). For this reason, it is difficult to visualize hormones as the regulators of the autosomal genes for index finger length.

A seemingly more plausible explanation as to how the sex of the individual determines which formula will be expressed in the heterozygous condition, is one which postualtes genes on the X-chromosome acting in such a manner as to bring about modification of genic expression, the degree of modification being dependent upon the number of X-chromosomes present. If factors on the X-chromosome act either to accentuate the action of the autosomal gene for a long index finger, I^L, or to inhibit to a certain degree the action of the gene for a short index finger, I^s, then their presence twice in the female and once in the

male would account for the difference in expression exhibited in the heterozygous condition by the two sexes. In accordance with this theory, a female with the genotype I^sI^L shows a formula of $2 = 4$ or $2 > 4$, whereas a male of the same genotype shows a phenotypic formula of $2 = 4$ or $2 < 4$. The dosage of the X-chromosome factor should also affect both of the homozygous conditions, such that two X-chromosomes in the genome have a greater effect than only one X-chromosome. Therefore, although both males and females who are homozygous I^LI^L have a $2 > 4$ formula, according to this theory the longest index finger found in females should be relatively longer than the longest index finger found in males. Conversely, although males and females both exhibit a $2 < 4$ formula when homozygous I^sI^s, the shortest index finger found in males should be relatively shorter than the shortest index finger found in females.

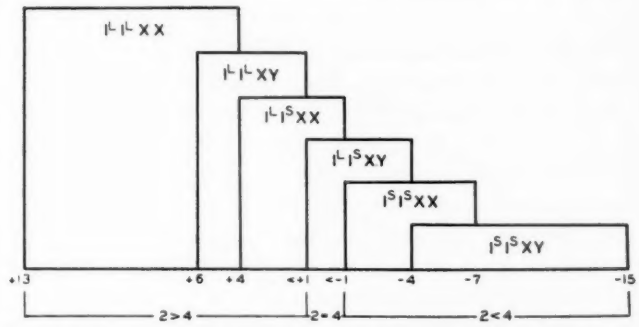

FIG. 2. Schematic diagram shows the way in which the sex of the individual is responsible for the differences in formula frequency in the two sexes. Modifying factors located on the X-chromosome act in such a way as to bring about modification of formula in both heterozygous and homozygous individuals, the degree of modification being dependent upon the number of X-chromosomes present. Thus in the heterozygous condition, females may have a long index finger formula and males, a short index finger formula; while in the homozygous condition, the longest index finger found among females is longer than any found among males, and conversely, the shortest index finger found among males is shorter than any found among females.

Corroboration for all aspects of this theory may be found in the data comprising the present study. The longest index finger found in the females projects 13 mm. beyond the end of the ring finger, while in males, the maximum projection was found to be only 6 mm. The shortest index finger found in the males is 15 mm. shorter than the ring finger, while in the females, the minimal projection is only 7 mm. When the proportion of heterozygous individuals is calculated on the basis of gene frequencies, the upper limit of difference for a heterozygous female appears to be +4 mm., whereas the lower limit for heterozygous males approximates −4mm. The relationship between the genes for the sex-influenced trait and the number of X-chromosomes is postulated to follow the pattern diagramed in figure 2.

It must be pointed out in conclusion that the scheme presented above for

the inheritance of relative index finger length is only a tentative one and subject to further modification as more data are collected and the action of the genes concerned is better understood. The occurrence of two family histories which do not seem to follow the postulated mode of transmission is probably not indicative of the inaccuracy of the scheme as now proposed, but may be due to the occurrence of mutation or to over-simplification resulting from the postulation of only a single sex-linked modifying gene (or gene complex) for length. If, however, the sex-influenced modification is the result of dosage effect of one or more pairs of sex-linked alleles which differ in the degree of their modifying effect, then the theoretical discontinuity of index finger length in the population, as based on genotypic frequency, would more closely approximate the observed phenotypic continuity of index finger length variability.

SUMMARY

Three formulas of index finger length may be discerned in the human hand: index finger shorter than ring finger; index finger equal in length to ring finger; and index finger longer than ring finger. The $2 < 4$ formula is the most frequent one among males, while a $2 > 4$ formula predominates among females. Population gene frequency analysis shows that the frequency distribution of formulas in the two sexes is in conformity with that of a sex-influenced trait, wherein the gene for a short index finger behaves as a dominant in the males and as a recessive in the females. In most of the family histories investigated, the phenotypes of the parents and offspring, and the frequencies with which the phenotypes occur in the offspring, are in agreement with the theory of sex-influenced inheritance.

Differences in formula are due to variations in the length of the index digit which are independent of metacarpal or ray length and general body build. The various formulas can be observed as early as the end of the seventh week of fetal life. Hormones do not appear to be responsible for the sex difference in index finger length since the formulas are established before the period in which hormone production is initiated. It is suggested that a modifying factor located on the X-chromosome acts in such a manner as to bring about modification of index finger length in both heterozygous and homozygous individuals, the degree of modification being dependent upon the number of X-chromosomes present.

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Familial Leukemia: A Report of Three Cases of Leukemia and One Leukemoid Reaction in One Family[1]

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REPORTS on the occurrence of familial human leukemia can be found in the literature as far back as 1872. However, it is only comparatively recently that geneticists have attempted to ascertain the possible hereditary basis for this disease. The most successful results have been obtained from breeding experiments with mice.

MacDowell (1934–5) conducted extensive studies and concludes that in spontaneous leukemia of a highly susceptible, homologous strain of mice, extrinsic factors determine which small per cent will not develop the disease. When a male of a highly susceptible strain (90%) is crossed with a non-leukemic strain, about half the F_1 develop leukemia. The extrinsic factors play a greater role while hereditary tendencies to leukemia are reduced. These hybrid males when backcrossed to the negative strain produce offspring in which the leukemic incidence is reduced to about half that in the F_1.

Cole and Furth (1941) carried out a series of crosses between two inbred strains of mice, one with 70% lymphoid and the other with 2% myeloid leukemia and conclude that leukemia appears to be a polygenic dominant character with low penetrance, highly influenced by environment. Kirschbaum and Kaplan (1944) find that different strains of mice vary in their leukemic susceptibility to spontaneous leukemia, carcinogens and x-rays, the effective agents being determined by the strain of mice.

The study of the genetics of leukemia in man has proven a much more difficult task. In most of the reported cases of familial human leukemia only one or two members have been involved. There are however, eleven references known to the authors of three cases in one family and also six reports of four or more leukemics in one family[4]. Dameshek, Savitz and Arbor (1929) cite an

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[4] Recently Anderson (1951) has reported leukemia in five siblings, with relevant genetic considerations.

interesting case of chronic lymphatic leukemia occurring in identical Jewish twins aged 56. The disease ran a parallel course in the two and they died within two months of each other.

In the family studied by us (Fig. 1) there are 3 definite cases of leukemia and one with an unusual blood picture which we call a leukemoid reaction. The case summaries are as follows:

Case 1. Mrs. C. H. K. was 26 years old when she was first seen in March 1934 with the chief complaint of enlarged abdomen which she had first noticed a year previously. The spleen was found to be greatly enlarged on physical examination. A blood count at this time showed 3,190,000 erythrocytes per cu. mm. and 325,000 leukocytes per cu. mm. The differential count included

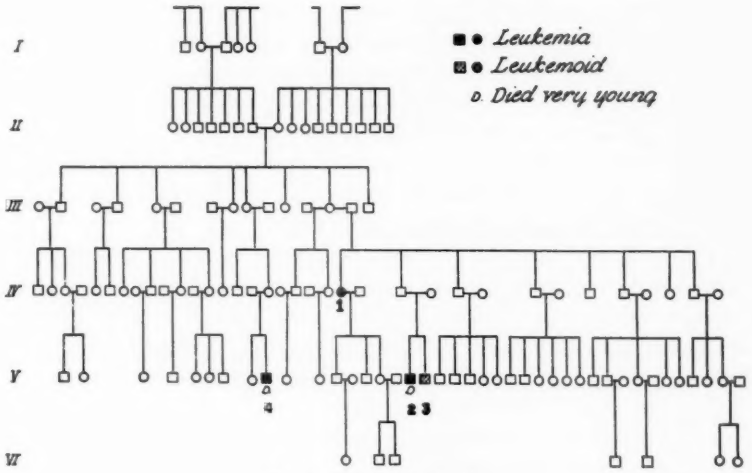

FIG. 1. Familial Leukemia

60% neutrophilic myelocytes, 4% eosinophilic myelocytes, 5% basophilic myelocytes, 5% metamyelocytes, 5% stab cells and 21% segmented forms; the blood film was confirmatory for chronic myleogenous leukemia. Repeated blood studies were made in the following years with no appreciable change in the blood picture. Multiple blood transfusions, colloidal lead and deep x-ray were given during the course of treatment. Gradual debilitation occurred and the patient expired June 1938.

Case 2. J. G. M. was first seen when 3 months old in 1929. At that time a diagnosis of acute lymphoid leukemia, based on clinical and hematological evidence was made. Splenomegaly had been pronounced at birth. The patient expired at 6 months of age. Laboratory records are not available.

Case 3. B. G. M., a brother of J. G. M., was found to have lymphadenopathy

at about one year of age and hepato-splenomegaly at that time. His blood count was 2,100,000 erythrocytes per cu. mm. with 45% hemoglobin and 2,300 leukocytes. The differential count included 12% segmented forms, 12% myelocytes, 28% eosinophils and 48% lymphocytes. He was diagnosed as chronic myelogenous leukemia. The patient has remained in fairly good health and at the present time is 18 years of age. The last count of which we have a record is 4,100,000 erythrocytes, 80% hemoglobin, 11,600 leukocytes, with a differential count of 44% segmenters, 3% myelocytes, 5% eosinophils, 10% monocytes and 38% lymphocytes on June 16, 1949. These previous blood films are not available for study by us and the patient has declined to have any further investigational blood studies. This case is considered by us to be a leukemoid reaction.

Case 4. D. C. D. was first seen in October 1950 when he was 21 months of age. An ophthalmologist was consulted at this time because of a proptosis of one eye. The blood findings showed an erythrocyte count of 3,190,000 per cu. mm. and a white cell count of 57,450 per cu. mm. Differential count included 6% polymorphonuclear neutrophils, 25% lymphocytes, 1% eosinophils, 26% myelocytes, 30% myeloblasts, 8% metamyelocytes and 4% stab cells. A diagnosis of acute myelogenous leukemia was made. The patient remained under medical care and expired in January 1951.

Discussion: The pedigree of the family in figure 1 shows that leukemia was absent for three generations before appearing in one individual in the fourth. This female mated with a non-leukemic male produced four normal offspring. A non-leukemic brother had two leukemic children while a cousin had two children, one of which developed leukemia. Case 2 was the first, chronologically, to develop leukemia. The family was brought to our attention when case 4 became ill, and to our knowledge has not been previously reported.

Most of the human familial leukemias described in the literature are of the lymphatic type. In the family described in this paper, cases 1 and 4 were of the myelogenous type of leukemia while 2 was acute lymphatic leukemia. Case 3 is thought by us to be a leukemoid reaction.

The data on the inheritance of human leukemia are still too sketchy for any definite conclusions to be reached. The different opinions expressed by various workers on the mode of inheritance demonstrate that no one simple gene mechanism is involved, but rather that in all probability different genes are concerned in the various types of leukemia. Videbaek (1947) in his monumental study of human leukemia concluded that no simple dominant or recessive gene was in action and that sex-limitation was not present. The simplest explanation for the inheritance of the cases described in the present paper may be based on the assumption of a recessive trait.

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The Geographic and Racial Distribution of ABO and Rh Blood Types and Tasters of PTC in Puerto Rico

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A LARGE number of studies (Boyd, 1939, Wiener, 1943) of population blood types frequencies have given the student of human variability a valuable tool for estimating group differences. This report,[1] from a sample of over 2,500 Puerto Rican adults, adds data to this already vast body of knowledge of world blood type and PTC non-taster frequencies. It also supplements data for Puerto Rico reported by Torregrossa (1945 a, b) for ABO and Rh frequencies. In addition to the report of island-wide frequencies, the variability of groups making up the total Puerto Rican population are examined. This intergroup analysis is based on a population breakdown according to racial phenotype and region of residence.

It is well known that within any human population random mating does not occur. Elements of human culture such as class structure, economic grouping, and the whole of social organization act to support and maintain selective systems. In addition, assortative systems of mating based on certain phenotypical characteristics are known to operate in human groups (Harris, 1930). Although the society and its attitudes and values set the pattern for these phenotype selection systems, the result is to reduce randomness of mating in a phenotypically varied population.

The Puerto Rican people, though less varied in origin than the population of the United States, have a development springing from lines originating in Southern Europe and Africa. In addition, the American Indian aborigines must have contributed a not inconsiderable genetic element which, though presently impossible to single out, may help to account for the island group heterogeneity for some characteristics.

Although mixtures between the originally quite distinct racial groups have gone on for a considerable time in Puerto Rico and even though it is said by

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[1] This paper reports on material gathered by the University of Puerto Rico Biological Survey which was a project in physical anthropology sponsored by the Social Science Research Center of the University of Puerto Rico. The field party consisted of Miss Joan Finkle, Mr. Rupert Murrill, and the author. Dr. H. L. Shapiro of the American Museum of Natural History acted as project supervisor. In addition, the author has been aided in carrying out statistical analysis by a research grant and a Summer Faculty Research Fellowship from the Rackham School of Graduate Studies of the University of Michigan.

many Puerto Ricans that race prejudice does not exist there, a rigid class structure and a strong and active system of race prejudice (Gordon, 1949–1950) have prevented the achievement of panmixia. In addition, the historical background of the migrations and economic pursuits of the various groups have acted so that the same proportions of the original groups have never existed in each of the various island regions. Even though Puerto Rico is a small island—a rectangle approximately 30 by 100 miles—and with considerable rates of internal migrations (U. S. Census Bull. #4, 1940), the regional differences have been maintained. Yet Puerto Rico cannot be considered unique in these respects, but probably is representative of many areas where immigration and subsequent race mixture has taken place.

The picture of significant genetic heterogeneity, if seen in Puerto Rico, would seem to indicate that population genetic surveys in other areas of the world should take into account phenotypic features that affect selective mating patterns and be based more often on representative samples. Otherwise the genetic characterization of whole populations on the basis of selected or conveniently gotten samples may be more misleading than constructive. In general, genetic surveys of populations should assume the existence of regional and social breeding isolates and should consequently give serious attention to insure that geographic and social sub-groups of the larger population are proportionally represented. Of course, the essential problem here is one of defining the population. Usually, however, due to cultural and historic features, we must work with groupings not readily definable or isolated. We are of necessity forced to work with given populations which need defining and description in terms of our problem. It would seem that random mating in human populations should not be assumed *a priori*, but follow a critical examination of the factors that may affect the frequency of each genetic characteristic studied.

METHODS

The sample reported here is a large portion of the total sample examined in the University of Puerto Rico Biological Survey, which studied the adult population of Puerto Rico during the period June 1948 to February 1949. In addition to the blood typing, 26 selected anthropometric measures, a dental record, several physiological characteristics, and some classificatory background material were noted for each individual. No comprehensive report of this project is yet published. The total sample of 3,562 adult Puerto Ricans (1,518 males, non-prisoners; 395 male prisoners; 1,649 females) was chosen according to a sample structure calculated before the survey began. On the basis of sex, age groups, and general economic status, the required number of individuals for each of 77 different municipios was calculated. A municipio is the area including and contiguous to a town and usually named for it. The municipio includes both urban and rural residences, and is highly variable

in size (populations from 169,247 to 860 for 1940) and densities (32,000 to 60 per square mile in 1940) of their population. Race was not used because the criteria employed in census enumeration are not clear for this.

The census data for 1935 and 1940 were used to extrapolate the numbers of the various categories which would be expected in June 1948. These calculations were provided through the courtesy of the Bureau of Vital Statistics of the Department of Health of the Government of Puerto Rico. The total numbers of adults between the ages of 20 and 45 inclusive was calculated as 744,693. The numbers for each of several age groups, residence categories, and sex and income groupings were calculated according to the 1940 proportions as applied to the new 1948 figure for each of the 77 island municipality regions. While this method of extrapolation has obvious deficiencies, it was a method of approximating the 1948 population structure which was considered better than using the 1940 figures. Where other information, such as the rates of increase resulting from the war, was known for specific localities, it was used in the calculations. An examination of the 1950 Census returns will ultimately test the accuracy of the 1948 predictions.

The sample structure thus calculated gives a representative sample of the whole island with each of the categories considered being included in our sample in the approximate proportion that they are found in the total population. Although this size sample (3,562) represents a little less than one-half of one per cent (0.48%) of the adult population and also, by being proportionally representative, gives very small numbers for some categories, the fact that no area or known social group was neglected gives a basis for determining island frequencies of observed characters and inter-population variability.

The sampling in each municipio was done so that no known bias favored the inclusion of any one segment of the population, and there is good reason to believe that the sample obtained is a random one within the categories selected. Because our sample gave proportions for urban-rural residence and nutritional background which match very closely known figures for Puerto Rico and because samples were gathered in each of the regions, we feel justified in assuming it to be representative.

Not all persons in the total sample of 3,562 were typed, nor were all that were typed for ABO also examined for Rh. Various difficulties in maintaining the supply of serum as well as the problem of getting blood to the typing laboratory in useable conditions made the number in the typed sample smaller. The number reported here does, however, represent the total numbers typed and none typed were not included. Because those not typed were not randomly spread through the sample, or not random by municipio, the blood type sample is not as accurately representative of the total population as the calculated sample. However, when the municipios are combined into regional districts, as has been done, no one section of the island is insufficiently represented in the

final sample. As will be noted later, the frequencies in a corrected sample designed to give the exact proportions of the calculated sample are not significantly different from the actual results (see table 12).

The regions used in this report are made up of ecologically similar municipios and these are listed in table 1. The location of the regions is indicated on the map in figures 1 and 2.

TABLE 1. MUNICIPIOS INCLUDED IN EACH OF THE 15 REGIONAL GROUPS

REGION NO.	MUNICIPIO
1	Aguadilla
	Camuy
	Hatillo
	Isabela
	Quebradillas
2	Arecibo
	Rio Piedras
	San Juan
3	Barceloneta
	Dorado
	Manati
	Toa Alta
	Toa Baja
	Vega Alta
	Vega Baja
4	Bayamon
	Catano
	Guaynabo
5	Carolina
	Loiza
	Rio Grande
	Trujillo Alto
6	Cieba
	Culebra
	Fajardo
	Humacao
6 (Con'd)	Luquillo
	Maunabo
	Naguabo
	Vieques
	Yabucoa
7	Arroyo
	Guayama
	Juana Diaz
	Patillas
	Penuelas
	Salinas
	Santa Isabel
8	Ponce
9	Guanica
	Guayanilla
	Lajas
	Sabana Grande
	Yauco
10	Coamo
	Villalba
11	Aguada
	Anasco
	Cabo Rojo
	Hormigueros
	Moca
	Rincon
	San German
12	Mayaguez
13	Adjuntas
	Ciales
	Jayuya
	Lares
	Las Marias
	Maricao
	San Sebastian
	Utuado
14	Aibonito
	Barranquitas
	Cayey
	Cidra
	Comerio
	Corozal
	Morovis
	Naranjito
	Orocovis
15	Aguas Buenas
	Caguas
	Gurabo
	Juncos
	Las Piedras
	San Lorenzo

The fifteen regions defined here were not chosen solely for this blood type frequency analysis but are the groupings used in the broader survey to denote similar environmental areas which also have a degree of historical similarity. Although a small island, Puerto Rico enjoys a wide range of geographical and climatic conditions. It was, in general, a total ecological viewpoint that decided the groupings. In addition, of course, the customary U. S. Census report units had to be used because their data made up the basis for the sample

structure. By combining various of the 15 regions listed here, the seven census regions used by the U. S. Census Bureau for reporting Puerto Rican demographic information can be constructed. It should be stated that the seven regions used in the U. S. Census reports were considered too inclusive and not representive of known ecological reality. The regional groups, then, do not represent a completely free approach to population grouping but were tied in with previous demographic report units. The dividing of the approximately 30 by 100 mile island into 15 regions gives reasonable certainty that population sub-group effects, if present, would be seen.

In addition to the geographic regional analysis, the population was sorted into phenotypically similar groups. The criteria used were those known (Gordon, 1950) to be held important by the Puerto Ricans themselves in assortative mating. These are skin color, hair form, nose shape and lip thickness. Inasmuch as the predominant racial groups constituting the present Puerto Rican population are White and Negro, these phenotypical characteristics also represent the most variable feature. Because the greatest preference, or social value, is given to skin color, with hair form, lip and nose characteristics being given less weight (Gordon 1949, 1950), these were evaluated accordingly in calculating the "ethnic factor" used in this report.

The system of calculating "ethnic factor" is as follows:

1. Skin color value was estimated by comparison with the von Luschan skin color scale. The range of recorded values was from 7 to 32, with 16 being the mean value for the total measured sample.
2. Hair form was judged visually and put in one category of a 5-point scale. The values for these positions were estimated and recorded as either 0, 4, 8, 12, or 16. Thus the values recorded into the "ethnic factor" total from hair form were approximately one half of those contributed by skin color.
3. Lip thickness and nose shape were judged on a 5-point scale and evaluated and recorded as either 0, 2, 4, 6, or 8. Thus these characteristics contributed approximately one half as much as hair form and one quarter as much as skin color in the total ethnic factor.

By adding up the values recorded for each of the four phenotypical characteristics, a total of from 7 to 64 was possible, the low number being the extreme White phenotype and the high number being the extreme Negro phenotype. This whole distribution range (7 to 64) was then evenly divided into 10 groups (0 to 9 inc.) with each individual being assigned to one group. These "ethnic groups" were then analyzed separately. It should be pointed out here that the sorting and typing procedure used here was not an attempt to place the individual racially but a mechanism to obtain a limited number of phenotypically similar groups. Inasmuch as the characters used are those most variable in a Negro-White mixed population, they do indicate the general racial affini-

ties of the groups. However, the individuals in the sample are not given a racial type on the basis of their ethnic factor. It is realized that the mode of inheritance or linkage between these characters is unknown, but it is assumed that within any one of these "ethnic groups" the genetic homogeneity is probably greater than in any combination of these groups, and certainly greater than in a combination of extreme groups. Also, because the characters used are the same ones given value by the Puerto Ricans in ascribing social status and influencing assortative mating, these "ethnic groups" have a valid use for this population. As will be seen in the genetic analysis which follows, these different phenotypical characteristics apparently have different values as group genetic "markers."

MATERIALS

The blood was drawn in a 10 cc. sample by veni-puncture. Five cc. were used in typing and five cc. used for other determinations not reported here. The samples were delivered to the Blood Bank Laboratory of the School of Tropical Medicine, where they were typed under the direction of Sr. N. Dobal[2] according to standard procedure recommended by Wiener (1943, 1946).

Difficulties were encountered with some of the sera used. Results from 3,079 MN determinations had to be discarded due to gross internal inconsistencies (test of binomality) in the frequency distribution of the types. Also the HR testing sera did not give consistent results so some 1,200 of these are also not reported.

In spite of these unfortunate difficulties, there is good reason to accept the reliability of the ABO and Rh frequencies here reported. In the first place, the results have internal consistency as seen in the $\frac{D}{\sigma}$ figures shown in tables 6 to 9; secondly, they are what would be expected from a Negro-White mixed population—that is, the Puerto Rican frequencies are intermediate to reported White and Negro figures.

For determination of the taster and non-taster reaction Phenyl-thiocarbamide crystals were placed by tooth pick applicator on the tongue of the 3,229 subjects tested. This method, while giving no indication of taste thresholds to known concentrations, does give all concentrations as the crystals dissolve and should discover all tasters. The infliction of this chemical on the palates of our trusting subjects gave the only threat to the otherwise excellent rapport

[2] Sr. Dobal was assigned to this study by the Director of the School of Tropical Medicine, Dr. Morales-Otero, and the considerable expense of laboratory analysis was carried by that institution. The sera were supplied by the Social Science Research Center of the Univeristy of Puerto Rico. The author wishes to express his gratitude and appreciation of the work done by Sr. Dobal and his assistants and to Dr. Morales-Otero for his unfailing assistance and encouragement in carrying this research to completion. Without his aid, this portion of our total project could not have been accomplished.

between investigators and Puerto Ricans during the study. It is unfortunate that so many were tasters.

BLOOD TYPING RESULTS

The number of individuals for the ABO system are reported by 15 regions in Table 2 and by 10 ethnic groups in Table 3. The Rh frequencies for 15 regions are given in Table 4 and for 10 ethnic groups in Table 5. The ABO gene frequencies, calculated by the square root formulae of Wiener (1943, 1945), together with calculation of the sum difference from 100 per cent and the

TABLE 2. DISTRIBUTION OF AGGLUTINOGENS A_1—A_2—B IN 15 REGIONS OF PUERTO RICO

REGIONS	CALCULATED SAMPLE NO.	TOTAL TYPED	% OF SAMPLE TYPED*	BLOOD GROUPS											
				O		A_1		A_2		B		A_1B		A_2B	
				N	%	N	%	N	%	N	%	N	%	N	%
1	183	177	97	107	60.45	46	25.99	11	6.21	12	6.78	1	0.56	0	0.00
2	726	644	89	322	50.00	173	26.86	66	10.25	64	9.94	9	1.40	10	1.55
3	188	220	117	115	52.27	48	21.82	34	15.45	20	9.09	1	0.45	2	0.91
4	128	68	53	36	52.94	16	23.53	4	5.88	11	16.18	1	1.47	0	0.00
5	120	250	208	133	53.20	62	24.80	11	4.40	36	14.40	4	1.60	4	1.60
6	220	223	101	129	57.85	52	23.32	15	6.73	24	10.76	1	0.45	2	0.90
7	240	246	102	136	55.28	53	21.54	26	10.57	24	9.76	4	1.63	3	1.22
8	199	152	76	84	55.26	35	23.03	12	7.89	17	11.18	0	0.00	4	2.63
9	150	76	51	38	50.00	17	22.37	9	11.84	9	11.84	2	2.63	1	1.32
10	59	48	81	36	75.00	6	12.50	3	6.25	2	4.17	0	0.00	1	2.08
11	196	174	89	86	49.43	58	33.33	19	10.92	8	4.60	3	1.72	0	0.00
12	150	204	136	111	54.41	46	22.55	22	10.78	20	9.80	3	1.47	2	0.98
13	274	252	92	137	54.36	64	25.40	22	8.73	24	9.52	1	0.40	4	1.59
14	267	270	101	141	52.22	77	28.52	33	12.22	17	6.30	1	0.37	1	0.37
15	233	241	103	141	58.51	53	21.99	25	10.37	21	8.71	1	0.41	0	0.00
Totals....	3333	3245	97	1752	53.99	806	24.84	312	9.61	309	9.52	32	0.99	34	1.05

* This column gives the percentage of the total calculated representative sample of Puerto Rico which was actually typed for ABO. The total sample was calculated to include 3333 individuals (3562 actually obtained) and the percentages given here are the proportion of the calculated sample of each region which were actually typed. 100% would be perfect correspondence.

probable error of the difference are given in Table 6 and 7. The Rh gene frequencies by region and ethnic groups are given in Table 8 and 9. Total island frequencies are given in Table 10. These total island frequencies for Rh are not significantly different from Torregrossa's (1945 a) report; however her sample was small. Table 10 includes Torregrossa's reported results.

If it is recalled that the lower ethnic group numbers are the White end of the range and the higher numbers Negro, the changes in gene frequencies in both the ABO and the Rh show gradiants which would be expected. In particular, the gradiant for R^o and for I^{A_1} and I^B show expected slopes. The fact

that the type O frequencies in Puerto Rico are high for both Negro and White ethnic groups may be attributable to the genetic contribution of the aboriginal

TABLE 3. DISTRIBUTION OF AGGLUTINOGENS A_1–A_2–B IN 10 ETHNIC GROUPS OF PUERTO RICO

ETHNIC GROUP	TOTAL TYPED	BLOOD GROUPS											
		O		A_1		A_2		B		A_1B		A_2B	
		N	%	N	%	N	%	N	%	N	%	N	%
0	6*	5	—	1	—	—	—	—	—	—	—	—	—
1	101	50	49.50	27	26.73	11	10.89	10	9.90	1	0.99	2	1.98
2	824	450	54.34	214	25.85	88	10.63	63	7.61	9	1.09	4	0.48
3	1441	787	54.61	382	26.51	136	9.44	112	7.77	8	0.56	16	1.11
4	433	224	51.73	109	25.17	40	9.24	50	11.55	6	1.39	4	0.92
5	133	70	52.63	26	19.55	9	6.77	22	16.54	5	3.76	1	0.75
6	159	89	55.97	28	17.61	14	8.81	24	15.09	1	0.63	3	1.89
7	101	54	53.47	15	14.85	10	9.90	18	17.82	1	0.99	3	2.97
8	42	23	54.76	4	9.52	3	7.14	10	23.81	1	2.38	1	2.38
9	1*	—	—	—	—	1	—	—	—	—	—	—	—
Totals...	3245	1752	53.99	806	24.84	312	9.61	309	9.52	32	0.99	34	1.05

* Frequences not listed because of insufficient sample size.

TABLE 4. FREQUENCIES OF THE RH BLOOD TYPES FOR 15 REGIONS OF PUERTO RICO

REGION	TOTAL TYPED	rh		rh′		rh″		rh′rh″		Rh_0		Rh_1		Rh_2		Rh_1Rh_2	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	150	15	10.00	0	0.00	1	0.67	0	0.00	20	13.33	70	46.67	24	16.00	20	13.33
2	326	24	7.36	2	0.61	0	0.00	0	0.00	41	12.58	163	50.00	59	18.10	37	11.35
3	212	26	12.26	3	1.42	0	0.00	0	0.00	41	19.34	99	46.70	21	9.91	22	10.38
4	51	5	9.80	1	1.96	2	3.92	0	0.00	6	11.76	25	49.02	6	11.76	6	11.76
5	244	25	10.25	7	2.87	1	0.41	0	0.00	48	19.67	114	46.72	28	11.48	21	8.61
6	177	16	9.04	0	0.00	0	0.00	0	0.00	31	17.51	90	50.85	29	16.38	11	6.21
7	212	17	8.02	7	3.30	1	0.47	1	0.47	37	17.45	113	53.30	18	8.49	18	8.49
8	126	11	8.73	1	0.79	2	1.59	0	0.00	13	10.32	58	46.03	18	14.29	23	18.25
9	61	5	8.20	0	0.00	1	1.64	0	0.00	8	13.11	25	40.98	12	19.67	10	16.39
10	31	6	19.35	1	3.23	0	0.00	0	0.00	4	12.90	13	41.94	4	12.90	3	9.68
11	154	13	8.44	1	0.65	0	0.00	0	0.00	16	10.39	70	45.45	28	18.18	26	16.88
12	191	10	5.24	1	0.52	1	0.52	0	0.00	16	8.38	109	57.07	33	17.28	21	10.99
13	253	21	8.30	3	1.19	0	0.00	2	0.79	14	5.53	124	49.01	38	15.02	51	20.16
14	209	20	9.57	2	0.96	3	1.44	0	0.00	18	8.61	98	46.89	34	16.27	34	16.27
15	131	8	6.11	2	1.53	0	0.00	0	0.00	21	16.03	65	49.62	22	16.79	13	9.92
Totals....	2528	222	8.78	31	1.23	12	0.47	3	0.12	334	13.21	1236	48.89	374	14.79	316	12.50

Indian element. In an attempt to follow this possibility, the blood type frequencies of those in the sample who had well defined shovel-shaped incisors, a characteristic of high frequency in American Indian groups, was analyzed. In

no way was this group, a sample of 424, significantly different from the total sample in either the ABO or Rh frequencies.

TABLE 5. FREQUENCIES OF THE RH BLOOD TYPES FOR 10 ETHNIC GROUPS OF PUERTO RICO

ETHNIC GROUP	TOTAL TYPED	rh		rh'		rh"		rh'rh"		Rh_0		Rh_1		Rh_2		Rh_1Rh_2	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0	6	0	0.00	0	0.00	0	0.00	0	0.00	1	16.67	3	50.00	1	16.67	1	16.67
1	84	4	4.76	0	0.00	0	0.00	1	1.19	4	4.76	52	61.90	10	11.90	13	15.48
2	635	58	9.13	2	0.31	5	0.79	1	0.16	64	10.08	315	49.61	102	16.06	88	13.86
3	1122	98	8.73	13	1.16	7	0.62	1	0.09	116	10.34	566	50.45	159	14.17	162	14.44
4	324	29	8.95	6	1.85	0	0.00	0	0.00	59	18.21	152	46.91	48	14.81	30	9.26
5	104	10	9.62	2	1.92	0	0.00	0	0.00	25	24.04	48	46.15	11	10.48	8	7.69
6	130	13	10.00	6	4.62	0	0.00	0	0.00	33	25.38	57	43.85	15	11.54	6	4.62
7	83	5	6.02	1	1.20	0	0.00	0	0.00	22	26.51	29	34.94	21	25.30	5	6.02
8	39	5	12.82	1	2.56	0	0.00	0	0.00	10	25.64	14	35.90	6	15.38	3	7.69
9	1													1	100.00		
Totals...	2528	222	8.78	21	1.23	12	0.47	3	0.12	334	13.21	1236	48.89	374	14.79	316	12.50

TABLE 6. ABO BLOOD GROUP GENE FREQUENCIES* FOR 15 REGIONS OF PUERTO RICO

REGION	GENE				TOTAL	DEVIATION FROM 100%	S. E.$_D$	$\frac{D}{\sigma}$
	I^O	I^{A1}	I^{A2}	I^B				
1	.777	.147	.039	.043	1.006	.006	.005	1.200
2	.707	.157	.069	.067	1.000	.000	.004	.000
3	.723	.123	.100	.060	1.006	.006	.006	1.000
4	.728	.140	.039	.103	1.010	.010	.014	.714
5	.729	.149	.030	.093	1.001	.001	.007	.143
6	.751	.134	.053	.077	1.015	.015	.007	2.143
7	.743	.124	.068	.063	0.998	.003	.006	.333
8	.743	.133	.052	.072	1.000	.000	.008	.000
9	.707	.132	.079	.079	.997	.003	.012	.250
10	.866	.067	.035	.024	.992	.008	.005	1.600
11	.703	.191	.074	.032	1.000	.000	.006	.000
12	.738	.130	.069	.063	1.000	.000	.006	.000
13	.737	.147	.057	.062	1.003	.003	.006	.500
14	.723	.161	.080	.042	1.006	.006	.005	1.200
15	.765	.123	.065	.055	1.008	.008	.005	1.600
Totals...	.735	.143	.062	.062	1.002	.002	.002	

* Gene frequencies calculated according to formulae given by Wiener (1943).

Regional differences are apparent in Tables 2 and 4, and give a picture of considerable variation. Region 10 stands out as a deviant one. To test the degree of homogeneity by regions, the Chi-Square test was applied. The formula used to calculate "t" was $\sqrt{2\chi^2} - \sqrt{2n - 1}$ (Fisher and Yates, Table IV, 1943). For the ABO distributions by region, the $\chi^2 = 69.99$ with d.f. 42, $t =$

2.72 so P is less than .01. Therefore, the distribution is non-homogeneous. For the Rh types, the same test was applied. The $\chi^2 = 135.32$ with d.f. = 70 gives $t = 4.66$, so again the distribution is definitely non-homogeneous.

TABLE 7. ABO BLOOD GROUP GENE FREQUENCIES† FOR 8 ETHNIC GROUPS OF PUERTO RICO

ETHNIC GROUP	GENE				TOTAL	DEVIATION FROM 100%	S. E.$_D$	$\frac{D}{\sigma}$
	I^O	I^{A1}	I^{A2}	I^B				
0*	—	—	—	—	—	—	—	—
1	.704	.156	.074	.067	1.001	.001	.013	.077
2	.377	.147	.068	.050	1.002	.002	.003	.667
3	.739	.151	.061	.050	1.001	.001	.002	.500
4	.719	.147	.062	.076	1.004	.004	.005	.800
5	.726	.118	.045	.106	.995	.005	.009	.556
6	.748	.103	.057	.095	1.003	.003	.008	.375
7	.731	.088	.065	.113	.997	.003	.011	.273
8	.740	.058	.047	.146	.991	.009	.016	.563
9*	—	—	—	—	—	—	—	—
Totals.....	.735	.143	.062	.062	1.002	.002	.002	

† Gene frequencies calculated according to formulae given by Wiener (1943).
* Frequencies not calculated because of small sample size.

TABLE 8. THE RH GENE FREQUENCIES* FOR 15 REGIONS OF PUERTO RICO

REGIONS	Rh GENE						TOTAL	DEVIATION FROM 100%	S. E.$_D$	$\frac{D}{\sigma}$
	r	r'	r''	R^0	R^1	R^2				
1	.3162	.0000	.0104	.1668	.3537	.1391	.9862	.0138	.0179	.771
2	.2713	.0110	.0000	.1752	.3824	.1073	1.0102	.0102	.0143	.713
3	.3501	.0198	.0000	.2120	.3110	.0822	.9751	.0249	.0102	2.441
4	.3130	.0299	.0574	.1513	.3575	.0885	.9976	.0024	.0325	.074
5	.3202	.0420	.0063	.2268	.3027	.0933	.9913	.0087	.0109	.817
6	.3007	.0000	.0000	.2146	.3645	.1399	1.0197	.0197	.0162	1.173
7	.2832	.0533	.0082	.2215	.3479	.0739	.9880	.0120	.0119	1.008
8	.2955	.0130	.0258	.1410	.3621	.1287	.9661	.0339	.0209	1.622
9	.2561	.0000	.0303	.1874	.3457	.1664	.9859	.0141	.0330	.427
10	.4399	.0353	.0000	.1280	.2767	.1040	.9839	.0161	.0291	.553
11	.2905	.0110	.0000	.1434	.3609	.1745	.9803	.0197	.0202	.975
12	.2289	.0111	.0112	.1402	.4637	.1803	1.0353	.0353	.0237	1.532
13	.2881	.0200	.0000	.0838	.4083	.1652	.9654	.0346	.0171	1.023
14	.3094	.0151	.0236	.1170	.3711	.1491	.9853	.0147	.0177	.831
15	.2470	.0292	.0000	.2235	.3564	.1534	1.0095	.0095	.0208	.457
Totals.....	.2956	.0202	.0079	.1729	.3605	.1336	.9907	.0093	.0147	

* Calculated according to formula given in Wiener, Zepeda, Sonn, and Polivka (1945).

In this test, Rh′, Rh″, and Rh′Rh″ were combined so that no numbers in the cells were zero. When this combining was not done, $t = 5.05$ resulted, compared to $t = 4.66$ in the combination.

At this point the obvious question is whether the lack of homogeneity is the result of there being different proportions of White and Negro in the various regions, inasmuch as the ABO and Rh frequencies do vary between these groups. Consequently, only persons of ethnic group 2 were put in one chi-square regional distribution and only those of ethnic group 3 in another. All 15 regions

TABLE 9. THE RH GENE FREQUENCIES* FOR 8 ETHNIC GROUPS OF PUERTO RICO

ETHNIC GROUP	Rh GENE						TOTAL	DEVIATION FROM 100%	S. E.$_D$	$\frac{D}{\sigma}$
	r	r'	r''	R^0	R^1	R^2				
1	.2182	.0000	.0000	.0903	.5366	.1543	.9994	.0006	.0355	.017
2	.3022	.0050	.0128	.1361	.3881	.1494	.9936	.0064	.0099	.646
3	.2955	.0190	.0103	.1412	.3850	.1349	.9859	.0141	.0072	1.958
4	.2992	.0295	.0000	.2200	.3206	.1266	.9979	.0021	.0110	.191
5	.3102	.0295	.0000	.2700	.2943	.0849	.9889	.0111	.0146	.760
6	.3162	.0662	.0000	.2786	.2547	.0902	1.0059	.0059	.0134	.440
7	.2454	.0233	.0000	.3250	.2350	.1901	1.0188	.0188	.0222	.847
8	.3581	.0341	.0000	.2621	.2227	.1136	.9906	.0094	.0238	.395
Totals.....	.2956	.0202	.0079	.1729	.3605	.1336	.9907	.0093	.0147	

* Calculated according to formula given in Wiener, Zepeda, Sonn, and Polivka (1945).

TABLE 10. PUERTO RICAN TOTAL ISLAND PERCENTAGE FREQUENCIES REPORTED BY TORREGROSSA (1945 A, B) COMPARED WITH THIS REPORT

Rh Blood Types

	rh	rh′	rh″	rh′rh″	Rh_0	Rh_1	Rh_2	Rh_1Rh_2	TOTAL TYPED
Torregrousa.....	10.1	1.7	0.5	0.00	15.1	39.1	19.6	14.0	179
Thieme.....	8.78	1.23	0.47	.012	13.21	48.89	14.79	12.50	2528

ABO Blood Types

	O	A	B	AB	TOTAL TYPED
Torregrossa.....	48.72	38.69	9.56	3.03	429
Thieme.....	53.99	34.45	9.52	2.04	3245

were used in all of these chi-square tests. The ABO and Rh distributions were as follows:

ABO

Ethnic Group 2 $\chi^2 = 55.00$ d.f. $= 42$ $t = 1.38$ $P = > 0.10$, Homogeneous
Ethnic Group 3 $\chi^2 = 47.84$ d.f. $= 42$ $t = 0.67$ $P = 0.50$, Homogeneous

Rh

Ethnic Group 2 $\chi^2 = 81.03$ d.f. $= 70$ $t = 0.97$ $P = > 0.10$, Homogeneous
Ethnic Group 3 $\chi^2 = 103.16$ d.f. $= 70$ $t = 2.57$ $P = 0.01$, Non-homogeneous

This gives us a test for the assumption that the ethnic groupings represent somewhat homogeneous genetic groups. In the above it will be seen that three

of the four groupings are homogeneous by the chi-square test and establishes that the assumption is correct to a degree. As a further test for this point, the test was applied to samples grouped by region for similar recorded categories of skin color, hair form, lip thickness and nose shape. The Rh distributions were used as they give a more rigorous test for homogeneity as can be seen above. The Chi Square test gave the following:

	Rh				
Skin Color	$\chi^2 = 88.77$	d.f. = 70	$t = 1.53$	$P = .126$,	Homogeneous
Hair Form	$\chi^2 = 105.53$	d.f. = 70	$t = 2.72$	$P = .0066$,	Non-homogeneous
Nose Shape	$\chi^2 = 109.44$	d.f. = 70	$t = 3.01$	$P = .0026$,	Non-homogeneous
Lip Thickness	$\chi^2 = 116.81$	d.f. = 70	$t = 3.49$	$P = .0005$,	Non-homogeneous

These results would seem to verify the statements made that skin color is the most important characteristic in determining mating choice in Puerto Rico, and that hair form is next in importance. This has acted to create group genetic similarity for other characteristics, in this case Rh frequency distributions. These results also tend to verify that skin color should be given the greatest importance in assessing ethnic factor and assortative mating, with hair form next, as was done from the outset in this study. In view of these results, doubt is cast upon the efficiency of the multiple character selection used in manufacturing an ethnic factor. It would seem that of the factors used, skin color alone would give a better sort into genetically homogeneous groups, as indicated by Rh blood type, than using all four combined. It is realized, of course, that this is for only one genetic constellation and would not necessarily hold for other genes.

As a demonstration of the well-known fact that the ABO and Rh frequencies vary by race, or by ethnic group as used here, chi-square tests for this were made. For the distribution of ABO types by the ethnic groups, the $\chi^2 = 54.30$, d.f. = 15, $t = 5.03$, $P = <0.0001$. For the Rh types, the results were also non-homogeneous, as $\chi^2 = 101.57$, d.f. = 25, $t = 7.25$ and $P = <0.0001$. In this test, ethnic groups 0 and 1, 5 and 6, and 7, 8 and 9 were combined so no cells would contain zero. And in the Rh test, Rh′, Rh″ and Rh′Rh″ were combined. This merely confirms the fact that different racial groups, in this case Negro and White, are characterized by different frequency distributions of the ABO and Rh blood types. It should be stated that, in all probability, each of the ethnic groups used here represents a mixed Negro-White group with the amount of mixture being less for the extreme group 0, 1, 2, and 7, 8, 9 than for the intermediate ones. It is difficult for any family long resident in Puerto Rico to point with certainty to a background lacking mixture. The rates of mixture were undoubtedly high during the early periods of colonization and slavery when Spanish women were scarce and Negro and Indian women were more plentiful. As in the United States, the Negro group in Puerto Rico has probably experienced considerable admixture since its arrival.

As a visual demonstration of the frequency distribution by regions, the island pattern for *r* and for non-taster is shown in figures 1 and 2. Approximately the same amount of variability by region would be found for genes I^O, I^A, I^B, R^2 and R^O. In addition, ethnic group comparisons would show even more dramatic differences. The results of tests of significance for inter-group regional and ethnic differences are not reported in detail because of the large number involved. Nevertheless, they do exist, even at the $P = .01$ level of significance. For example, when comparing the type O frequency of region 10 to region 2 and to region 9, the difference is significant in both cases. Also, significant differences are found for various blood types when comparing the total island

TABLE 11. FREQUENCY OF RH TYPES FOR PUERTO RICAN INDIVIDUALS BORN AND WITH PRESENT RESIDENCE IN 15 DIFFERENT GEOGRAPHIC REGIONS

REGIONS	rh		rh′		rh″		rh′rh″		Rh_0		Rh_1		Rh_2		Rh_1Rh_2	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	12	10.81	0	0.00	1	0.90	0	0.00	17	15.32	50	45.05	17	15.32	14	12.61
2	14	7.25	1	0.52	0	0.00	0	0.00	22	11.40	103	53.36	34	17.62	19	9.84
3	19	13.97	2	1.47	0	0.00	0	0.00	28	20.59	61	44.85	14	10.29	12	8.82
4	1	5.00	1	5.00	2	10.00	0	0.00	1	5.00	9	45.00	2	10.00	4	20.00
5	20	10.00	5	2.49	1	0.50	0	0.00	38	18.90	94	46.77	23	11.44	20	10.00
6	9	10.47	0	0.00	0	0.00	0	0.00	15	17.44	46	53.49	12	13.93	4	4.65
7	14	8.92	6	3.82	0	0.00	1	0.64	28	17.20	82	52.23	13	8.28	14	8.92
8	7	10.45	0	0.00	2	2.98	0	0.00	3	4.48	29	43.28	15	22.39	11	16.42
9	4	7.41	0	0.00	0	0.00	0	0.00	7	12.96	25	46.30	9	16.67	9	16.67
10	6	23.08	1	3.85	0	0.00	0	0.00	2	7.69	13	50.00	3	11.54	1	3.85
11	10	9.52	1	0.95	0	0.00	0	0.00	13	12.38	44	41.90	18	17.14	19	18.10
12	8	6.90	0	0.00	1	0.86	0	0.00	10	8.62	65	56.03	18	15.52	14	12.07
13	19	10.00	3	1.58	0	0.00	1	0.53	12	6.32	95	50.00	31	16.32	29	15.26
14	12	8.33	1	0.69	0	0.00	0	0.00	12	8.33	71	49.31	26	18.06	22	15.28
15	7	7.61	2	2.17	0	0.00	0	0.00	11	11.95	48	52.17	13	14.13	11	11.97
Totals.	162	9.54	23	1.35	7	0.41	2	0.12	218	12.84	835	49.18	248	14.61	203	11.96

sample frequency to various regional or ethnic sub-samples. The non-homogeneity indicated by the chi square results reported above confirms this general picture of island group variability.

In table 11, Rh frequencies for a sample selected according to different residence history are given. This group is composed of males and females who were born and remained in various geographic regions. They are the non-migratory segment of the total sample and represent the residual core of genetic material tending to perpetuate regional differences as they may occur. By visually comparing the frequencies shown here (table 11) with those given in table 4, some differences can be seen. Table 4 gives the total sample of all individuals classified by region of present residence regardless of island birth place. As a detailed Rh type by region comparison would involve the showing

of 120 "t" values, this is not included here. Yet it is apparent that significant differences between some regions in these two samples exist. Comparing the total island frequencies in each table, no significant difference occurs.

From this comparison, it would seem that individual migratory history may be an important sample consideration and that the inclusion of migrants may tend to reduce differences that actually exist between regions. This would be true for populations with a recent history of considerable internal migration. Of course, population with a long history of random internal migration would probably not be so affected. The chi square test applied to the distribution given in table 8 gives the following results compared to table 3:

Table 8 $\chi^2 = 109.54$ d.f. $= 70$ $t = 4.66$ $P = 0.00006$
Table 3 $\chi^2 = 135.32$ d.f. $= 70$ $t = 3.18$ $P = 0.0014$

It might be expected that the non-migrants would show greater heterogeneity by virtue of their representing existing isolates historically originated and unaltered by the high rates of recent internal migration. However, this is not the case as indicated by this test. Random migration is not characteristic of Puerto Rico, where localized and limited economic opportunity are motivating individual movements within prescribed spheres. How this may affect frequencies of particular genes is not answered here, except to say it apparently has no effect on Rh frequencies.

A check was performed to see whether the actual sample, by virtue of not being an exact duplicate of the calculated representative sample (see table 2), could have introduced a significant deviation which would affect the representativeness of the total island frequencies shown in table 7. To do this each region's proportions of ABO and Rh were applied to extrapolate its actual sample up or down in the calculated sample size. The proportions of types for each region remained unchanged but as between regions they were changed. These extrapolated numbers for each region were then used to calculate the total island frequencies based on a sample of 3,333, the total calculated sample. Table 12 gives the results of this comparison. None of the differences shown is significant so the actual sample obtained is used as the basis for comparisons in this report.

TASTER (P. T. C.) RESULTS

Non-taster percentage frequencies are given in table 13 by regions and in table 14 by ethnic groups. These are the same groupings used for blood type analysis.

The sub-group heterogeneity is not significant. The chi-square test gives the following results for males only:

Ethnic groupings: $\chi^2 = 9.63$ d.f. $= 7$ $P = 0.20$
Regional Groupings: $\chi^2 = 19.71$ d.f. $= 14$ $P = 0.10$

The females more frequently taste than do the males, yet the difference is not significant at the 5% level ($t = 1.54$). However, this difference is not constant between males and females by ethnic group. The difference is less

TABLE 12. COMPARISON OF TOTAL ACTUAL SAMPLE WITH TOTAL CALCULATED SAMPLE FOR FREQUENCIES OF ABO AND RH TYPES.

ABO

	O	A_1	A_2	B	A_1B	A_2B
Calculated	53.88	24.88	9.70	9.49	1.01	1.04
Actual	53.99	24.84	9.61	9.52	.99	1.05
Difference	+.11	−.04	−.09	+.03	−.02	+.01

Rh

	rh	rh′	rh″	rh′rh″	Rh_0	Rh_1	Rh_2	Rh_1Rh_2
Calculated	8.53	1.16	0.46	0.11	12.82	48.75	15.46	12.71
Actual	8.78	1.23	0.47	0.12	13.21	48.89	14.79	12.50
Difference	+.25	+.07	+.01	+.01	+.39	+.14	−.67	−.21

TABLE 13. FREQUENCY FOR MALES AND FEMALES OF NON-TASTERS OF P.T.C. FOR 15 REGIONS OF PUERTO RICO

REGIONS	MALES			FEMALES		
	Total Tested	Non-Tasters	% Frequency	Total Tested	Non-Tasters	% Frequency
1	80	10	12.50	86	6	6.98
2	299	59	19.73	265	29	10.94
3	151	19	12.58	100	11	11.00
4	35	2	5.71	27	1	3.70
5	126	18	14.29	121	6	4.96
6	120	12	10.00	98	7	7.14
7	98	13	13.26	151	16	10.60
8	90	13	14.44	115	21	18.26
9	62	9	14.52	11	2	18.18
10	32	5	15.63	38	4	10.53
11	97	8	8.25	65	8	12.31
12	99	12	12.12	86	10	11.62
13	139	15	10.79	141	15	10.63
14	140	19	13.57	123	13	10.57
15	125	11	8.80	109	9	8.26
Totals	1693	225	13.29	1536	158	10.29

for the Whites than for the Negro. This suggests that a possible difference in penetrance between the sexes, which might explain this difference, may be unequal in different races; and here, specifically, between persons of African

and European origin. In addition, the relatively low non-taster frequency found in Puerto Rico (see tables in Boyd, 1950, and Gates, 1946) suggests again the presence of American Indian in the make-up of the present population. However, Lee (1934) gives a frequency of 9.2% for non-tasters in the American Negro, which is under the figures reported here. Consequently, any interpretation pointing to the effects of the American Indian strains in Puerto Rico is doubtful from this evidence alone. Yet, the historical records give clear evidence that this is a plausible explanation in the case of Puerto Rico because significant numbers of American Indians were present there in colonial times.

TABLE 14. FREQUENCY FOR MALES AND FEMALES OF NON-TASTERS OF P.T.C. FOR 10 ETHNIC GROUPS OF PUERTO RICO

REGIONS	MALES			FEMALES		
	Total Tested	Non-Tasters	% Frequency	Total Tested	Non-Tasters	% Frequency
0	2	0	0.00	—	—	—
1	40	5	12.50	44	4	9.09
2	377	43	11.40	441	53	12.02
3	818	113	13.81	671	68	10.13
4	216	29	13.43	208	21	10.10
5	58	9	15.58	68	5	7.35
6	83	6	7.23	61	4	6.56
7	63	12	19.04	35	3	8.57
8	36	8	22.22	7	0	0.00
9	—	—	—	1	0	0.00
Totals.....	1693	225	13.29	1536	158	10.29

DISCUSSION

The frequency of the ABO and Rh blood types in Puerto Rico, as well as non-tasters of P. T. C., is as would be expected in a mixed Negro-White-American Indian population. However, variability within this population is significant. It seems that the general implications of this are quite clear. Specifically, sampling for genetic traits in a population must be done in a fashion which will measure the internal variability and sample all groupings to give an overall representative result. It is also indicated from these findings that at least regional and phenotypic sub-groups must be representatively sampled before any remarks about the gene frequencies of a population are valid.

In this study, the genetic variability of the Puerto Rican population is shown to be large (see figures 1 and 2). Consequently, if the sample had been gotten from one region, rather than from all, the results may have been significantly different. For example, if region 10 had been the sole scene of sampling, the obtained type O frequency would have been 21.01% more than that

actually obtained. To put it another way, the frequencies of type O (see table 2 and 4) may have been from 49% to 75%, for type A_1 from 12% to 33%, for rh from 5% to 19% and for Rh_1 from 41% to 57%, if the sample had been

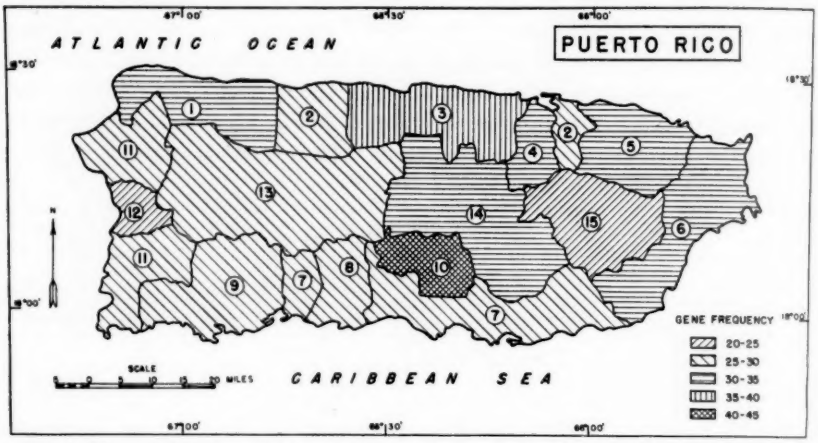

FIG. 1. The gene frequency distribution for *r* in the population of Puerto Rico for 15 geographic regions.

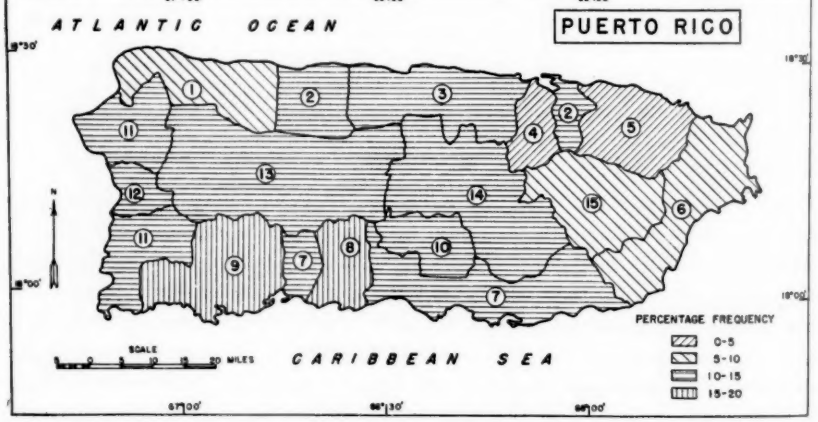

FIG. 2. The percentage frequency of male non-tasters in the population of Puerto Rico by 15 geographic regions.

obtained only from certain regions. From this, it seems evident that a sample derived from one region probably would have given quite different results. Although some of the regions did turn out to be representative of the frequencies for the whole island, this fact was not known, nor could it be known, until

the total representative sample had been gathered. Now we know which regions are typical in terms of certain genetic frequencies, but this, of course, does not mean that they will be typical for other traits. There seems to be no escaping the task of obtaining a representative sample if our problem is to determine the population genetic frequency.

In a review of the literature in blood type frequencies, no reports based on pre-determined demographically representative samples has been found. Although it is readily acknowledged that some reported samples may truly be representative, it cannot be verified from procedures reported that this is so. It would seem that reliable demographic information is available for many populations of the world—at least as these populations are defined by national boundaries—and consequently, the efforts in the future should direct attention both to the definition of the population and to its representative genetic description. It is also important to emphasize the need for valid sampling in terms of choice of subjects. As Glass remarks in commenting on a paper by the author (Thieme, 1950), the difficulty of obtaining valid samples in blood typing laboratories, hospitals or clinics is very great. Any selection such as must obviously underlie such samples does not give us the picture of the total population which is ultimately desirable. In the last analysis, we can seldom hope that findings from studies carried out for one problem will give answers to different problems. Clinics, hospitals and insurance company examinations are not designed to gather representative population data. They may approach this goal but the degree of attainment should be measured, not assumed. To the same extent, the results of blood group surveys on people about which demographic knowledge is lacking must be viewed with caution. Continental maps with isogene lines showing large trends for changes in gene frequencies by areas are occasionally based on small samples and frequently on unrepresentative samples. The standard error of estimates for small samples is large and frequently so large as to overlap the range of variation seen in any one of the isogenic maps for a continent. It is not necessary to belabor the need for large numbers in sampling, or the desirability of representativeness. Most investigators are aware of this. However, it is apparent that this desirable goal for all studies is far from being achieved.

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A Study of the Genetics of Diabetes Mellitus[1]

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THERE IS universal agreement that there is a large hereditary component in the causation of diabetes mellitus. In fact Joslin, in the "preamble" to Chapter 3 of the eighth edition of *The Treatment of Diabetes Mellitus*, makes the statement that "Heredity is the basis of diabetes." Disagreement arises, however, when an attempt is made to describe the genetic nature of this component. Further on in this same preamble Joslin indicates this uncertainty when he writes, "Would that experts in the genetic field would become interested in this problem."

The preamble is followed by a section written by White and Pincus in which they present an excellent review of the literature as well as of their analysis of data gathered in Joslin's clinic.

As illustrations of the disagreement which exists we may refer to the studies, involving sizable numbers of histories, of some workers who have come to quite different conclusions. Thus Cammidge (1928 and 1934) classified individual family pedigrees according to whether they could more readily be explained as resulting from a dominant or from a recessive gene. He concluded that the disease in those individuals with early onset and severe manifestation tended to be due to a recessive gene and that in those individuals with late onset and a mild expression, the disease tended to be due to a dominant gene (these genes were assumed to be at different loci). Hanhart (1950 and earlier), using the same method of analysis, maintained that all pedigrees may be explained by assuming a single recessive gene.

Pincus and White (1933) concluded from their analysis of the pedigrees of 523 diabetic and 153 nondiabetic patients that the data could be satisfactorily explained by assuming that the disease is due to a single recessive gene. However, Levit and Pessikova (1934) concluded from their analysis of 222 pedigrees

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that diabetes is due to a dominant gene with a penetrance of about 10 per cent and Harris (1950) has suggested, as a result of the analysis of data concerning the relatives of 1,241 diabetics, that "Many of the late-onset mild cases could be regarded as heterozygous for a gene which, in homozygous form, gives rise to the early-onset severe type of case." Penrose and Watson (1945) studied the sibs and parents of 442 patients with at least one affected relative and reported a sex-linked tendency in familial diabetes in a significant proportion of the families.

A priori we should expect that diabetes is genetically heterogeneous, as indeed many investigators have claimed. Such a situation is, of course, well known for many hereditary diseases in man as well as in other animals and plants. It also is well known that, despite genetic heterogeneity in some diseases, most of the cases are the result of one type of genetic change, as for example in albinism (Pipkin and Pipkin, 1942). It is possible that such is the situation with respect to diabetes mellitus.

THE MATERIAL

The material on which this report is based consists of information gathered over a two-year period by interviewing 1,981 consecutive patients at the Mayo Clinic who had the diagnosis of diabetes mellitus entered on their record for the first time during the current visit. Information concerning the patient's parents, sibs, spouse, and children was collected on a special form designed for this study.

We have no illusions concerning the accuracy of the information we have obtained. There are undoubtedly errors with regard to the ages of relatives, the presence or absence of diabetes, and the ages at onset. It is probable that there are inaccuracies with regard to the reporting of consanguinity between the patient's parents and between the patient and his spouse. In brief, we believe that every kind of error in reporting which could be made has been made in these data. However, we have exerted every effort to keep these errors to a minimum and, short of interviewing and examining every individual mentioned in each of these 1,981 pedigrees, we know of no way of obtaining more accurate data. We shall assume, as have all our predecessors, that the errors of reporting are random or at least are not sufficiently biased to disturb our conclusions.

THE DATA

Age at Onset.—The age at onset for those patients who were aware of their diabetes before they came to the clinic is the age reported by the patient. We do not know whether that age is the age at diagnosis or at detection of first symptoms. The possible error here is a compound one in that it involves the difficulty inherent in determining the age at onset plus the inaccuracy associ-

ated with an attempt to recall the time of an event which may have occurred long ago. This group composed 83 per cent (1,646/1,981) of the total sample. The remaining 17 per cent (335/1,981) did not know they had diabetes when they came to the clinic. The age at onset for this group of patients is reported as the age at diagnosis. This method of recording tends to increase the reported age at onset by an unknown margin depending on how long the disease may have been present and undiagnosed. The mean age at onset for the males in this group is 57 years and for the females 55 years, as contrasted with 46 and 45 years for the males and females in the group composed of those who knew of their diabetes prior to coming to the clinic.[4]

Table 1 shows the distribution of the ages of the 1,981 probands at onset. A Chi-square comparison of the age distributions of the male and female

TABLE 1. AGE OF PATIENT AT ONSET OF DIABETES

AGE, YEARS	TOTAL		MALES		FEMALES	
	Number	Per cent	Number	Per cent	Number	Per cent
0–9	51	2.57	23	2.02	28	3.33
10–19	107	5.40	59	5.18	48	5.70
20–29	134	6.76	81	7.11	53	6.29
30–39	230	11.61	125	10.98	105	12.47
40–49	455	22.98	267	23.44	188	22.33
50–59	603	30.44	340	29.85	263	31.24
60–69	336	16.96	201	17.65	135	16.03
70–79	60	3.03	39	3.42	21	2.49
80–89	5	0.25	4	0.35	1	0.12
Total.....	1,981	100.00	1,139	100.00	842	100.00
Average age at onset, years.....	47		48		47	

patients indicated that the distributions were not significantly different ($X^2_{[7]} = 8.048$; $P > 0.3$). The mean ages at onset were 48 years for the 1,139 males, 47 years for the 842 females, and 47 years for the combined total of 1,981 patients. We note here for future reference that the mean age at onset is essentially the same regardless of whether neither, one, or both of the patient's parents were diabetic, these ages being 47, 48 and 45 years respectively.

Table 2 presents a comparison between the present age of the patient and the age at onset for males and females separately. The correlation between these

[4] It is interesting to note that only 780 (47 per cent) of the 1,646 patients who were aware of their diabetes before coming to the clinic came because of their diabetes or its associated symptoms. Even more striking is the fact that only 59 (18 per cent) of the 335 whose diabetes was first diagnosed during their visit to the clinic came because overt symptoms of diabetes were present. None of the preceding values are influenced by the sex of the patient.

ages is high and essentially the same for both males and females, as is indicated by a comparison of the average present ages recorded in the extreme right columns for each decade of age at onset.

The relation between the age of the patient and of his affected parent at onset is presented in table 3. We present the data to make them available and shall not discuss them in detail because Harris (1950) has already shown that the apparent correlation is spurious and we have shown in two previous publications (Steinberg and Wilder, 1950 and in press) that the apparent "anticipation" is also spurious. There is nothing in the present data that contradicts either of these conclusions.

TABLE 2. AGE AT ONSET VERSUS PRESENT AGE OF PATIENT

AGE AT ONSET, YEARS	PRESENT AGE, YEARS									TOTAL	AVERAGE PRESENT AGE, YEARS
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89		
Males											
0–9	11	4	7	1						23	14
10–19		19	15	18	4	2	1			59	28
20–29			24	32	19	5	1			81	36
30–39				51	46	23	4	1		125	44
40–49					133	91	37	6		267	52
50–59						240	91	9		340	58
60–69							182	18	1	201	66
70–79								38	1	39	75
80–89									4	4	85
Total	11	23	46	102	202	361	316	72	6	1,139	
Females											
0–9	10	8	10							28	15
10–19		21	19	7		1				48	23
20–29			26	17	6	4				53	33
30–39				35	36	25	9			105	46
40–49					82	88	16	2		188	52
50–59						169	89	5		263	59
60–69							121	14		135	66
70–79								21		21	75
80–89									1	1	85
Total	10	29	55	59	124	287	235	42	1	842	

The relationship between the age of the patients and of their affected sibs at onset is shown in table 4. The correlation coefficient derived from these data is 0.549, which, while significantly lower than the value found by Harris (1950), 0.695 ($P < .01$), is significantly greater than zero. Harris showed that a large portion but not all of this high value of the correlation coefficient was due to the correlation which exists between the ages of sibs. Hence, most of the sibs

of the patients with early age of onset are still young and therefore could not have a late onset of diabetes. However, after correction for correlation due to this there remained a significant, but much lower, correlation between the age of the patient and of the affected sib at onset. The reality of this correlation may be illustrated in another more indirect way by reference to the data of

TABLE 3. RELATION BETWEEN AGE OF PATIENT AND AGE OF DIABETIC PARENT AT ONSET

AGE OF PATIENT AT ONSET, YEARS	AGE OF PARENT AT ONSET, YEARS								
	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Total	Not stated
0–9			1					1	
10–19	1	1	1	2	3			8	
20–29	2	4	4	2	2	1		15	3
30–39		4	12	14	7	4	2	43	9
40–49		2	23	25	33	16	3	102	20
50–59		2	7	32	26	12	6	85	26
60–69		2	3	16	12	7	2	42	9
70–79				2	2	1		5	2
Total.....	3	15	51	93	85	41	13	301	69
Average age of patient, years...	22	39	42	50	49	48	51	48	49

TABLE 4. RELATION BETWEEN AGE OF PATIENT AND AGE OF DIABETIC SIB AT ONSET

AGE OF PATIENT AT ONSET, YEARS	AGE OF SIB AT ONSET, YEARS										
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Total	Not stated
0–9	1	4								5	1
10–19	2	4	1							7	0
20–29	3	6	7	7	3	5	1			32	5
30–39		1	7	10	18	7	1			44	12
40–49		2	4	16	37	33	17	2		111	25
50–59	1		9	10	26	59	18	5		128	32
60–69		2	3	5	13	30	26	5		84	12
70–79					1	5	5	1	1	13	1
Total.....	7	19	31	48	98	139	68	13	1	424	88
Average age of patient, years.	24	26	42	44	48	53	57	59	75	49	49

table 10 (which will be referred to again), in which it can be seen that the frequency of diabetes among the sibs of patients with early onset is as great as that among the sibs with late onset. This could arise only if a correlation existed between the age of patient and sib at onset.

While the existence of the correlation is clear its biological meaning is far

from being so. It is possible that a large portion of the correlation arises from peculiarities of establishing the presence of diabetes. For example, if diabetes is diagnosed in a child or young adult living at home, it is probable that others in the home will be examined for diabetes. Therefore, even mild diabetes, which might otherwise continue for a long time before diagnosis, would be detected soon after its onset. Among older persons who had already left home this would be less likely to occur. Other factors are the probable greater accuracy of knowledge of sibs when the patient is young than when the patient is old and the greater similarity of environment between the patients and sibs when the patient is young. The problem requires an intensive investigation of the

TABLE 5. BIRTH ORDER OF PATIENT VERSUS FAMILY SIZE

FAMILY SIZE	BIRTH ORDER														TOTAL
	1	2	3	4	5	6	7	8	9	10	11	12	13	16	
2	117	113													230
3	87	98	86												271
4	79	63	56	67											265
5	54	67	48	53	56										278
6	45	47	42	33	36	36									239
7	20	24	30	32	20	28	31								185
8	18	17	16	24	22	21	15	21							154
9	15	14	10	13	14	15	10	8	8						107
10	5	7	4	7	11	9	7	2	5	12					69
11	3	3	3	6	1	1	3	3	3	3	5				34
12	3	2	1	1	3	3	2	7	1	0	1	1			25
13	0	2	1	0	0	0	1	1	1	0	1	3	2		12
14	0	0	0	0	1	0	1	0	0	0	0	0	0		2
15	1	0	0	0	0	1	0	0	0	0	0	0	0		2
16	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
18	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Total observed...	447	457	297	236	164	114	71	42	18	15	7	4	2	1	1,875
Expected.....	438.1	438.1	323.1	232.7	166.5	110.9	71.0	44.6	25.3	13.4	6.5	3.4	1.3	0.1	

method of ascertaining the age at onset in the different families. It has characteristics in common with those encountered in "anticipation" and may very well have no greater biological significance than was shown to be the case for "anticipation" (Steinberg and Wilder, 1950 and in press).

Birth Order.—The data in table 5 show the birth order of the patients versus the number of children in the family who have survived the first year of life. (The 106 patients who had no siblings are not included in this table.) Only those who survived the first year of life are included because diabetes rarely occurs during the first year and therefore those not surviving this period are considered not to have been exposed to the risk of diabetes.

These data may be used to test the association between birth order and susceptibility to diabetes. If there is no association between susceptibility to diabetes and birth order, the expected number of patients in each birth order position for each family size is simply the number of families of the indicated size divided by that size. Thus there are 230 families of 2 children each; hence the number of patients expected for each birth order is 230/2 or 115.0. This process is repeated for each family size and then the contributions of each family size to birth order 1, birth order 2, 3, and so on, are summed. It is these sums which are entered on the bottom row of table 5. A X^2 comparison of the observed and expected values indicates that they are not significantly different ($X^2_{[11]} = 6.771$; $P \leqq 0.80$). It may be concluded that there is no correlation between birth order and susceptibility to diabetes.

Sex Ratios.—There were 1,139 male patients (57.5 per cent) and 842 female patients (42.5 per cent). The presence of an excess of males among diabetic patients, while not usual in the findings of other large studies, is not entirely

TABLE 6. SEX OF PATIENT VERSUS THAT OF AFFECTED PARENT OR SIB

PATIENT	AFFECTED RELATIVE				
	Parent*		Sib		
	Male	Female	Male	Female	Not stated
Male	89	114	147	121	2
Female	61	106	118	121	3
Total	150	220	265	242	5

* Only cases with 1 parent affected are included.

unique (Levit and Pessikova, 1934; Cammidge, 1934; Dahlberg and associates, 1947; and others), and furthermore is consistent with previous reports from this clinic (Wilder, Browne and Butt, 1940; Berkson, Gage and Wilder, 1947). Because the last paper cited contains a discussion of the possible reasons for this difference and because the subject will be dealt with in extenso elsewhere, it will not be discussed further here.

The relation between the sex of the patient and that of his affected parent or sib is shown in table 6. There is no indication of a significant association between the sex of the patient and that of the affected parent ($X^2_{[1]} = 2.033$; $P > 0.10$) nor between that of the patient and the affected sibs ($X^2_{[1]} = 1.510$; $P > 0.20$). However, we should like to call attention to the excess of affected mothers. The frequency of females among the affected parents (59.5 per cent) is significantly greater than that among the patients ($P < 0.001$). While we cannot account for this finding, we suggest that it may be due in part at least to a higher effective fertility among female diabetics as contrasted to male diabetics or to the patients' greater knowledge of their mothers than of their fathers or to a combination of these reasons.

Genetic Analysis.—Table 7 shows the number of affected offspring (patient and sibs) versus family size separated into three groups based on whether none, one or both parents were diabetic. From this table the average size of family and the frequency of diabetes among the patients' sibs may be computed for each of the three groups. The figures are presented in table 8. The large average

TABLE 7. NUMBER OF DIABETIC OFFSPRING (INCLUDING PATIENT) VERSUS FAMILY SIZE

FAMILY SIZE	NEITHER PARENT DIABETIC							ONE PARENT DIABETIC							BOTH PARENTS DIABETIC				
	Number of diabetic offspring							Number of diabetic offspring							Number of diabetic offspring				
	1	2	3	4	5	6	Total Fam.	1	2	3	4	5	7	Total Fam.	1	2	3	4	Total Fam.
1	91						91	13						13	2				2
2	178	7					185	40	2					42	3				3
3	201	19	1				221	39	6	4				49	1				1
4	190	21	6	2			219	35	6	3				44	2				2
5	192	16	8	1	1		218	36	12	9				57	2		1		3
6	152	34	4				190	33	11	3				47	1	1			2
7	113	31	1			1	146	14	13	4	3	2		36			1	2	3
8	95	20	4	1	1		121	17	9	5		1		32	1				1
9	65	7	3	1	1		77	15	7	3	1		1	27		2	1		3
10	34	17	4	1	1		57	6	3			1		10	1	1			2
11	13	10	4	1			28	2	2	1	1			6					
12	14	4	2				20	1		2	1	1		5					
13	4	6					10	1		1				2					
14	2						2												
15	1			1			2												
16	1						1												
18	1						1												
Total....	1,347	192	37	8	4	1	1,589	252	71	35	6	5	1	370	13	4	3	2	22

TABLE 8. AVERAGE FREQUENCY OF DIABETES AMONG SIBS OF PROBAND AND AVERAGE FAMILY SIZE VERSUS NUMBER OF DIABETIC PARENTS

NUMBER OF PARENTS DIABETIC	MEAN FAMILY SIZE	SIBS		
		Total	Diabetic	
			Number	Per cent
0	5.2	6,664	311	4.7
1	5.4	1,620	185	11.4
2	5.6	100	16	16.0

family size (5.2, 5.4, and 5.6 when none, one or both parents respectively are affected) is striking, particularly when it is recalled that only those individuals who survived the first year of life are included in the study. However, if it is noted that most of the families are completed (only 4 per cent of the patients were less than 20 years old and 1 per cent were less than 10 years of age [table

2]) and that most of them were completed more than a generation ago (only 17 per cent of the patients were less than 40 years of age [table 2]) and that a large proportion are rural families, the figures are not quite so surprising.

The average size of family does not appear to be reduced by the presence of diabetes among one or both parents, at least for those diabetic parents who have had one or more diabetic children. The same conclusion may be drawn from Pincus and White's and from Harris' data. In Pincus and White's sample the average number of offspring per family was 4.4 when neither parent was diabetic and 4.7 when one was (no figures are available for the 2 or 3 families with both parents affected) and in Harris' sample the values are 4.0, 4.4, and 5.4 when neither, one, or both parents respectively are diabetic. While in both sets of data the average family sizes are somewhat smaller than ours they show, as do ours, that the average size of family is not reduced by the presence of diabetes in one or both parents. Indeed, when all three sets of data are considered there is a suggestion that the average size of family may be increased when diabetes occurs in one or both of the parents. These remarks, naturally, are pertinent only to that group of diabetic parents who have produced at least one diabetic child and most probably are not correct as generalizations for all diabetics (Miller, 1946; Barns and Morgans, 1948).

The assumption of a single dominant gene with incomplete penetrance (Levit and Pessikova, 1934) is not consistent with the fact that in our sample, diabetes is more than twice as frequent among the sibs when one parent is diabetic than when neither parent is diabetic, nor is it consistent with the similar findings of Pincus and White (1933) and Harris (1950). Levit and Pessikova did not consider this point nor did they present their data in a manner which would permit others to consider it. If a dominant gene with incomplete penetrance were the correct explanation, the presence of overt diabetes in one parent would not be expected to increase the frequency of diabetes among the patients' sibs.

Harris (1950) suggested that "Many of the late-onset mild cases could be regarded as heterozygous for a gene which, in homozygous form, gives rise to the early-onset severe type of case. The distribution of the homozygous and heterozygous cases, both in respect to age at onset and to severity, would be presumed to overlap to a certain extent. There would be incomplete manifestation, particularly of the heterozygotes. . . ." As is customary, Harris considers early onset as onset prior to age 30 years.

On the basis of this hypothesis, when onset is prior to age 30 years both of the patient's parents should be heterozygotes (we are assuming that none of the parents were homozygotes; see later) with the exception of the parents of an undefined number of patients who, although they became diabetic prior to age 30 years, are overlaps in the sense that they are heterozygotes with early onset. For the present purposes these overlaps may be ignored. When onset

in the patient is after age 30 years it is possible that both parents are heterozygotes, although in the usual case only one will be.

None of the parents in the 22 matings between affected individuals had onset prior to age 30 years and only 1 had onset prior to age 40 years. The 3 affected parents with onset prior to age 30 years (table 3) were all married to nondiabetic individuals. Hence if we disregard overlaps among the parents none of the matings involved homozygotes.

If we assume random mating the frequencies of the two types of realized matings (as already stated, we are considering the 3 parents with early onset as heterozygotes) which yield heterozygotes may be determined as follows: Let p equal the frequency of D, the gene leading to a susceptibility to diabetes, and $q = (1 - p)$ = frequency of d, its normal allele.

MATING	FREQUENCY	OFFSPRING		
		dd	*Dd*	*DD*
(1) *Dd* × *dd*	$4\ pq^3$	$2\ pq^3$	$2\ pq^3$	
(2) *Dd* × *Dd*	$4\ p^2q^2$	p^2q^2	$2\ p^2q^2$	p^2q^2

The relative frequency of heterozygotes from matings 1 and 2 equals q/p. With this ratio if we know the value of p we can compute the proportion of heterozygotes to be expected among the parents of patients who became diabetic after age 30 years. We do not know the value of p; however, we may safely assume that it does not exceed 0.5. If it equals 0.5 the ratio $q/p = 1$ and therefore equal numbers of heterozygotes are derived from matings 1 and 2 and consequently the proportion of heterozygotes among the parents of heterozygotes equals 0.75. If we assume a more reasonable value for p, say 0.10, the expected proportion of heterozygotes among the parents is 0.55. It follows therefore that the frequency of heterozygotes (affected parents) among the parents of patients with late onset of diabetes should be somewhat less than that among the parents of patients with early onset. The data are presented in table 9. In both sets of data (Harris' and the present sample) approximately twice as many diabetics occur among the parents of patients with late onset as among the parents of those with early onset.[5] This, of course, is exactly the reverse of the prediction.

If Harris is correct, the frequency of diabetes among the sibs of patients with onset prior to age 30 years should be greater than among the sibs of pa-

[5] Part of this excess is due to the fact that the parents of patients with late onset are older than those with early onset. However, the data of the present sample still show a higher frequency of diabetes among the parents of the patients with late onset after an approximate correction for this age difference based on the method used by Pincus and White (1933). The "corrected" values are 11.1 per cent for the parents of patients with early onset of diabetes and 17.5 per cent for those of patients with late onset of diabetes.

tients with onset after age 30 years because, as was already pointed out, most of the patients with early onset are homozygotes and therefore come from matings in which both parents are heterozygotes, while most patients with onset after 30 years are heterozygotes and are derived from matings which are mostly between a heterozygote and a normal. Furthermore, and very importantly, these frequencies should not be affected by the presence or absence of overt diabetes in one of the parents. The data are presented in table 10. Again we find that the data are not in agreement with the prediction. In both sets of data the frequency of diabetic sibs is the same, within statistical limits,

TABLE 9. FREQUENCY OF DIABETES AMONG PARENTS OF PATIENTS WITH EARLY AND LATE ONSET OF DIABETES

PATIENT'S AGE AT ONSET	PER CENT OF DIABETIC PARENTS	
	Harris' data	Present sample
Less than 30 years	3.3	5.0
30 years and more	6.2	11.4

TABLE 10. FREQUENCY OF DIABETES AMONG SIBS OF PATIENTS WITH EARLY AND LATE ONSET OF DIABETES

PATIENT'S AGE AT ONSET	ALL SIBS		NEITHER PARENT DIABETIC		ONE PARENT DIABETIC	
			Sibs		Sibs	
	Total	Per cent diabetic	Total	Per cent diabetic	Total	Per cent diabetic
Harris' data						
Less than 30 years	1,019	4.1	971	3.5	48	18.8
30 years and more	2,773	4.4	2,446	4.1	327	10.7
Present sample						
Less than 30 years	828	6.0	736	5.0	92	14.1
30 years and more	7,456	6.0	5,928	4.6	1,528	11.2

regardless of the age of the patient at the onset of diabetes, but in each age group the frequency of diabetic sibs is significantly greater when one parent is diabetic than when neither parent is diabetic.

Harris (1949) reported an excess of consanguinity among the parents of patients with early onset of diabetes but not among the parents of those with late onset. This excess was established by comparing his observed values with those found by Julia Bell (1940) in a survey of the hospital population of England. The over-all rate of consanguinity among the patients' parents which she found was 0.8 per cent. Among the diabetics in her sample she found 1.3

per cent with consanguineous parents, Harris found 1.5 per cent in his sample, and we find 1.8 per cent in our sample. This includes all degrees of consanguinity and patients of all ages. Table 11 shows a breakdown of our data. We have no base line with which to compare our data; however, we may note that there were no known marriages between first or second cousins among the parents of the patients with early onset and that the total rate of consanguinity was not higher among the parents of those with early onset than among those with late onset. The excess consanguinity observed by Harris occurred among the marriages of cousins of a degree higher than first cousins. In the present sample the frequency of consanguineous marriages of other than first degree among the parents of patients with diabetes of early onset is 1.4 per cent and for the parents of those with late onset 1.1 per cent. The comparable figures in Harris' sample are 1.2 and 0.3 respectively. We might examine the data differently by using Wright's (1922) coefficient of relation-

TABLE 11. CONSANGUINITY AMONG PARENTS

AGE OF PATIENT AT ONSET	CASES	DEGREE OF CONSANGUINITY									
		First cousins		Second cousins		Other cousins		Consanguinity unspecified		Total	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Less than 30 years	292	0		0		2	0.7	2	0.7	4	1.4
30 years and more	1,689	12	0.7	7	0.4	8*	0.5	4	0.2	31	1.8
Total	1,981	12	0.6	7	0.4	10*	0.5	6	0.3	35	1.8

* One first cousin once removed.

ship, which computes the probability that an autosomal gene present in one individual will also be present in a specified relative by virtue of their common ancestry. The coefficients of relationship for the relationships pertinent to our discussion are as follows: Uncle-niece (one case in Harris' data) 1/4; first cousin, 1/8; first cousin once removed, 1/16; second cousin, 1/32 and third cousin, 1/128. To avoid fractions we shall set the coefficient for third cousins equal to 1 and change the others so that they retain their same relative values and then use these values to weight the observed frequencies of consanguineous marriages (all marriages not specified as to degree are considered third cousin marriages, as are all marriages more distant than those between second cousins), and calculate an average coefficient of relationship. The results are shown in table 12. The mean value is about ten times greater for the parents of patients with late onset than that for the parents of patients with early onset. In Harris' data the former value is about sixteen times as great as the latter (0.179 to 0.011). We may conclude that there is no very strong evidence

to indicate a greater frequency of consanguineous marriages among the parents of patients with early onset of diabetes as compared to that which occurs among the parents of those with late onset.

The possibility remains, however, that there is an increase in consanguinity among the parents of diabetics. This would be consistent with an hypothesis which assumes, as did Pincus and White (1933) and others, that diabetes is due to a single recessive gene. Another requirement of such an hypothesis is that the ratio of the frequencies of affected siblings derived from the three types of matings which yield recessive offspring (neither parent [$Aa \times Aa$], one parent [$Aa \times aa$], both parents [$aa \times aa$] affected) be as 1:2:4. This is true of conditions which are present congenitally. In a disease such as diabetes in which the age at onset is so variable the best we can expect is an approximation of these values, the closeness of the approximation depending in part on the age distributions of the offspring from each of the matings. In the present sample (table 8) these values are in the ratio of 1:2.4:3.4, which we

TABLE 12. AVERAGE RELATIVE VALUE OF COEFFICIENT OF RELATIONSHIP

AGE OF PATIENT AT ONSET	CASES	RELATIVE VALUE OF COEFFICIENT OF RELATIONSHIP	
		Total	Mean
Less than 30 years	292	4	0.014
30 years and more	1,689	239	0.141
Total	1,981	243	0.123

consider a reasonable approximation of the expected ratios. A third general requirement of this hypothesis is that the age of onset shall not be influenced by the presence or absence of diabetes in the parents. We have already noted (pp. 115 and 117) that the average ages at onset in the patients were essentially the same regardless of the presence or absence of diabetes in the parents.

While it is necessary that data fulfill these three conditions to fit a single-gene hypothesis, fulfilling them is not sufficient to prove that the hypothesis is in agreement with the data. An additional test is to derive numerical expectations and examine the closeness of the fit of these to the data. One approach, the one used by Pincus and White, is to correct for the variable age of onset of the disease and for the age distribution of the sibs; a second is to derive an expected frequency for each of the three types of mating which yield recessives and to compare the data with these values. We shall apply the latter method to our data and to those of other investigators.

This method of analysis assumes (1) that mating is random with respect to diabetes, (2) that all types of matings yielding diabetics are equally fertile and (3) that ascertainment is essentially equal for the matings that yield

diabetics. We have no evidence for the first assumption, pro or con, but it seems reasonable because most marriages occur before the onset of diabetes. The second assumption is known to be wrong when all diabetics are considered; however, as was shown in an earlier portion of the paper, fertility is equal among those matings which have yielded at least one diabetic offspring, therefore the assumption may be considered reasonable for our data. The third assumption offers no difficulty for the present sample because ascertainment is at a minimum.

On the basis of these assumptions if we assume that the diabetics are homozygous recessives and allow p to equal the frequency of the gene leading to diabetes and $q = (1 - p)$ to equal the frequency of its normal allele we can derive the proportions of all diabetics expected from each of the three types of matings, and from this we can estimate the value of p and test the fit of the observed data to the expected values. (Allan [1933] used a very similar

TABLE 13. EXPECTED FREQUENCIES OF MATINGS YIELDING DIABETICS, PROPORTION OF DIABETICS IN TOTAL POPULATION OF OFFSPRING AND PROPORTION OF DIABETICS ARISING FROM EACH MATING

MATING	1	2	3 = 2/p^2
	Frequency	Frequency of recessives in total population	Proportion of recessives arising from given mating
Neither parent diabetic	$4p^2q^2$	p^2q^2	q^2
One parent diabetic	$4p^3q$	$2p^3q$	$2pq$
Both parents diabetic	p^4	p^4	p^2

technic;[6] however he used a value of p obtained from an independent estimate of the frequency of diabetes in the population as a whole, and because this estimate yielded a high value of p, the deviations between the observed and expected values were considerable [$X^2_{(2)} = 7.064$, $P < 0.05$]. Consequently his cautious conclusion was, "... it seems possible that diabetes may be transmitted as a recessive unit character." We have analyzed his data by the method to be described presently and find that they do not differ significantly from the expected frequencies [table 14].) The details are shown in table 13. The maximum likelihood solution for p, using the values of column 3, is $\hat{p} = \frac{b + 2c}{2N}$ where b equals the observed number of matings in which one parent was diabetic, c equals the observed number in which both parents were diabetic, and N equals the total number of matings. (This, of course, is the frequency of diabetes among the parents.) In the present sample $p = (370 + 2[22])/2(1{,}981) = 0.1045$; in Pincus and White's sample $p =$

[6] See also the theoretical discussion in Dahlberg and Hultkranz (1927).

$(80 + 2[3])/2(523) = 0.0822$; in Allan's sample $p = (17 + 2[2])/2(143) = 0.0734$, and in Harris' sample $p = (109 + 2[8])/2(1,241) = 0.0504$. These values of p may be used to compute the expected frequencies in each of the four samples of each of the three types of matings which yield recessives, namely, q^2, $2pq$, and p^2 when neither, one or both parents, respectively, are diabetic. The derived values and their comparison with the observed values are shown in table 14. The fit to our data, Pincus and White's and Allan's data is remarkably good, but Harris' data differ significantly from the expected values. We have no explanation of why Harris' sample is so different from the other three; however, Harris' sample was not a random one in that he selected for his purposes a disproportionately large number of cases with early onset of diabetes, and it may be because of this that the observed and theoretical values differ so greatly (see Steinberg and Wilder, in press, for further comment on Harris' sample).

TABLE 14. COMPARISON OF EXPECTED FREQUENCIES OF MATINGS YIELDING DIABETIC OFFSPRING WITH OBSERVED FREQUENCIES FOR FOUR SETS OF DATA

MATING	PRESENT SAMPLE		PINCUS AND WHITE		ALLAN		HARRIS	
	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed
Both parents diabetic....	21.6	22	3.6	3	0.8	2	3.1	8
One parent diabetic.....	370.8	370	78.8	80	19.4	17	118.8	109
Neither parent diabetic..	1,588.6	1,589	440.6	440	122.8	124	1,119.1	1,124
$X^2_{(1)}$.....	0.009		0.119		2.109		8.573	
P.....	>0.90		>0.70		>0.10		<0.01	

DISCUSSION

On the basis of the preceding analysis it seems clear that neither the assumption of a dominant gene with incomplete penetrance nor the assumption that those persons with early onset of diabetes are homozygous for a gene which in the heterozygous condition leads to a late onset of diabetes is consistent with the data of our sample, or with those of the authors who made the original assumptions. The only single-gene hypothesis which is consistent with the several sets of the data is that a predisposition to diabetes is inherited as a simple recessive. Thus we confirm the conclusion advanced by Pincus and White in 1933. This, it seems to us, eliminates the necessity for assuming genetic heterogeneity of the type suggested by Cammidge (1934). We did not find, as did Penrose and Watson (1945), evidence of a sex-linked tendency in a significant proportion of the families; on the other hand, our data do not rule out the possibility that such a tendency may exist in some of the families.

We should like to emphasize that we do not believe that all cases of geneti-

cally determined diabetes are due to a simple recessive gene. Indeed, evidence exists in the literature (Burnstein and Patterson, 1949, as a recent example) and in our own files that in occasional pedigrees the disease is due to a dominant gene. Furthermore, it is not established that all cases due to a simple recessive gene are due to a change at the same locus. We do believe, however, that, as in albinism, the vast majority of the cases are due to a simple recessive mutation at one particular locus.

The method of analysis used in the previous section of the paper affords an estimate of the frequency of diabetes in the country as a whole if it is assumed that our sample is representative of the diabetics in the nation. This frequency (p^2) is 1.09 per cent of diagnosed diabetics in the present population. The estimate based on Pincus and White's sample is 0.68 per cent. The estimate based on their data is expected to be lower than the one based on ours because their sample was drawn approximately twenty years before ours was—that is, at a time when the population was relatively younger than it is now.

If a correction is made for the variable age at onset of diabetes and the age distribution of the population from which the sample was drawn, an estimate of the frequency of the gene in the population as a whole may be obtained. The corrected frequencies should be essentially the same for the two samples. Using the age distribution of the white population of the United States of the 1920 census to correct Pincus and White's sample, which was collected in 1932, and the population of the 1940 census to correct our data, which were collected over a two-year period beginning in May, 1949, and following the procedure used by Pincus and White, we obtain corrected values of $p = 0.22$ and 0.24 for the two samples respectively.

If these estimates of p are accepted as satisfactory we can predict that the total of diabetics (potential, undiagnosed and diagnosed) constitutes about 5 per cent of the population. In an earlier paragraph the frequency of diagnosed diabetics was estimated as about 1 per cent; hence there are approximately four times as many potential and undiagnosed diabetics in the population as there are diagnosed diabetics. As the average age of the population increases we may expect more diabetics to occur until the frequency of diabetics in the population approaches 5 per cent.

The estimates offered in preceding paragraphs reemphasize the importance to preventive medicine of gaining an understanding of the factors which cause a potential diabetic to become a frank diabetic.

The problem of explaining the variable age of onset of diabetes remains; in essence, this is the problem just referred to. Since most, if not all, diabetics are homozygous for the same recessive gene, the source of this variability must be sought at other loci and in the environment. If the correlation between the age of sibs at onset should prove to be of biologic significance, it would strongly suggest the presence of genetic modifiers affecting the time of

onset of the disease. A detailed longitudinal study of twins and of individuals with both parents diabetic could shed much light on this problem.

SUMMARY

1. The data concerning 1,981 consecutive diabetic patients and the information obtained from them concerning their parents and sibs were analyzed.

2. The modal age at onset was during the age interval 50–59 years for both male and female patients. The mean ages were 48 and 47 years respectively. The mean age at onset was not affected by the presence of diabetes in one or both parents.

3. No relation was found between birth order and susceptibility to diabetes.

4. No relation was found between the sex of the patient and that of his affected parent or sib. However, there is among the diabetic parents a significant excess of affected mothers.

5. The average size of family is not affected by the presence of diabetes in one or both parents, at least for those diabetic parents who have had one or more diabetic children.

6. The frequency in percentage of diabetes among the patients' sibs when diabetes is present in neither, one or both parents is 4.7, 11.4 and 16.0, respectively, in the ratio of 1:2.4:3.4. These figures are uncorrected for age.

7. The frequency of diabetes among the patients' parents is 10.45 per cent.

8. There is evidence of a possible increase of consanguinity among the parents of diabetics. The total rate of consanguinity was 1.8 per cent, and the frequency of marriages of first cousins was 0.6 per cent.

9. It is shown that only the hypothesis of a simple autosomal recessive gene is consistent with the data of this sample as well as those of some other published large samples.

10. It is estimated that the frequency of this gene lies between 20 and 25 per cent and that potential, diagnosed and undiagnosed diabetics constitute about 5 per cent of the population, while diagnosed diabetics form about 1 per cent of the population.

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APPENDIX

TABLE A. AGE OF NONDIABETIC PARENTS: MATINGS IN WHICH BOTH WERE NONDIABETIC

AGE OF PATIENT AT ONSET, YEARS	AGE OF PARENT, YEARS*										
	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90 and more	Not stated	Total
Mother											
0–9		4	18	17	8	3					50
10–19			9	33	31	20	3	2		1	99
20–29		2	5	12	41	36	16	3			115
30–39			10	12	33	57	45	12	2	1	172
40–49	1	6	17	21	35	74	102	53	10	6	325
50–59		5	28	40	50	106	121	113	17	5	485
60–69		4	13	18	23	50	76	87	11	3	285
70–79		1	4		3	8	14	17	6		53
80–89			1			2	1	1			5
Total.....	1	22	105	153	224	356	378	288	46	16	1,589
Father											
0–9		1	16	17	10	6					50
10–19			6	27	33	24	8	1			99
20–29		1	2	13	33	42	19	4		1	115
30–39		2	7	12	38	43	47	20	2	1	172
40–49		2	6	17	44	74	108	59	9	6	325
50–59		5	15	32	59	95	143	108	18	10	485
60–69		3	7	9	21	46	106	76	12	5	285
70–79			1	1	5	6	19	17	4		53
80–89						1	2	1	1		5
Total.....		14	60	128	243	337	452	286	46	23	1,589

* Present age if living, age at death if dead.

TABLE B. AGE OF NONDIABETIC PARENT: MATINGS IN WHICH ONE PARENT WAS DIABETIC

AGE OF PATIENT AT ONSET, YEARS	AGE OF PARENT, YEARS*									
	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90 and more	Not stated	Total
Mother										
10–19			1	2	1					4
20–29				4	3	1	1	1		10
30–39		1		5	8	7	1			22
40–49		2	2	2	18	22	3	1		50
50–59		3	1	6	6	15	7	2		40
60–69		1	2	2	4	6	5	1		21
70–79				1				2		3
Total.....		7	6	22	40	51	17	7		150
Father										
0–9			1							1
10–19			1	1	2					4
20–29				2	4	2				8
30–39		2	1	5	9	8	4		1	30
40–49	1		3	11	22	22	11	2		72
50–59		3	1	13	19	22	13			71
60–69		1	3	4	7	4	9	1	1	30
70–79						3	1			4
Total.....	1	6	10	36	63	61	38	3	2	220

* Present age if living, age at death if dead.

TABLE C. AGE OF PARENTS AT ONSET OF DIABETES VERSUS AGE OF ONSET IN PATIENT: BOTH PARENTS DIABETIC

AGE OF PATIENT AT ONSET, YEARS	AGE OF PARENT AT ONSET, YEARS							
	30–39	40–49	50–59	60–69	70–79	80–89	Not stated	Total
Mother								
20–29		1						1
30–39	1		1	3	1			6
40–49		1	3	1	2		1	8
50–59		1	4		1		1	7
Total	1	3	8	4	4		2	22
Father								
20–29				1				1
30–39		1	1	2	1	1		6
40–49			2	1	1	1	3	8
50–59		1		3	1	1	1	7
Total		2	3	7	3	3	4	22

TABLE D. AGE OF ONSET OF DIABETES IN SIBS OF PATIENTS

AGE OF PATIENT AT ONSET, YEARS	AGE OF SIB AT ONSET, YEARS										
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Not stated	Total
Neither parent diabetic											
0–9	1	3								1	5
10–19	2	3	1								6
20–29	2	4	4	5	2	5				4	26
30–39		1	4	5	12	4	1			10	37
40–49		1	4	7	18	16	13	2		8	69
50–59	1		4	4	13	44	12	4		14	96
60–69		1	1	1	10	16	20	4		10	63
70–79						2	4	1	1	1	9
Total	6	13	18	22	55	87	50	11	1	48	311
One parent diabetic											
0–9		1									1
10–19		1									1
20–29	1	2	3	2	1		1			1	11
30–39			3	4	5	1				2	15
40–49		1		9	18	16	4			14	62
50–59			5	6	8	14	5	1		18	57
60–69		1	2	4	3	14	6	1		2	33
70–79					1	3	1				5
Total	1	6	13	25	36	48	17	2		37	185
Both parents diabetic											
30–39				1	1	2					4
40–49					1	1				3	5
50–59					5	1	1				7
Total				1	7	4	1			3	16

TABLE E. PRESENT AGE* OF NONDIABETIC SIBS

AGE OF PATIENT AT ONSET, YEARS	AGE OF SIBS, YEARS											
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90 and more	Not stated	Total
Neither parent diabetic												
0–9	25	30	27	11	1							94
10–19	31	50	91	63	23	5	2	3				268
20–29	15	25	82	118	56	34	12					342
30–39	18	26	54	199	225	97	43	11	2			675
40–49	67	28	62	214	351	364	211	55	4			1,356
50–59	100	51	75	121	392	712	498	120	13		4	2,086
60–69	82	34	48	45	103	313	399	204	34	3	2	1,267
70–79	10	5	13	12	8	35	72	65	19		1	240
80–89		3		3		4	7	7	1			25
Total...	348	252	452	786	1,159	1,564	1,244	465	73	3	7	6,353
One parent diabetic												
0–9		1	2									3
10–19	1	2	7	8	3							21
20–29	2	3	7	21	16	3	3					55
30–39	13	5	16	49	64	46	14					207
40–49	25	16	23	91	144	118	51	13				481
50–59	27	7	19	36	89	168	96	23				465
60–69	11	3	3	4	16	74	53	23				187
70–79				1	1	2	5	7				16
Total...	79	37	77	210	333	411	222	66				1,435
Both parents diabetic												
20–29			1									1
30–39		1	7	8	8	8	2					34
40–49	1			2	20	8	1					32
50–59	1		1		7	6		2				17
Total...	2	1	9	10	35	22	3	2				84

* Present age if living, age at death if dead.

Twin and Sibship Study of Overt Male Homosexuality[1]

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Of the vast number of structural and functional components essential in human personality development, very few are more urgently in need of an understanding of the basic phenomena of physiological genetics than is true regarding the differentiation of sexual behavior. Irrespective of the methodological procedure used in an approach to the formation of variable behavior patterns, the sex function is certain to emerge as the axis, around which the personality is organized (2). It is not surprising, therefore, that it is the various forms of sex behavior, which have been vulnerable to rather preposterous misapplications of that ancient dichotomy perpetuated in the presumably antithetic setting of the nature-nurture controversy. The consequence has been that in many contemporary post-graduate classes, an allusion to a possible relationship between sex and organic inheritance is unlikely to provoke more than a polite smile of skepticism.

With respect to homosexuality, one of the most pretentious means of disclaiming any interaction of genetic elements in the causation of deviant behavior patterns appears to rest quite safely upon the tenet that no gene can be assumed to be capable of determining the final choice of a sex partner. As an advocate of modern principles of human genetics, one may be given an opportunity to mention that no special gene is suspected of being able to produce a potential preference for saccharine in persons predisposed to diabetes mellitus. However, the end of this kind of argument is usually reached with a repetitive denial of the existence of "any inheritable qualities in the structuralization of the sex potentiality that would direct a person either away from a member of the same sex or toward the opposite sex" (10).

From a genetic standpoint, it is rather inappropriate to separate the object from the quality of a person's sexual striving. Evidently, neither aspect can be

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[1] This report was presented at the annual meeting of the American Society of Human Genetics in Minneapolis (September 10–12, 1951) and was the second on the progress of a study, which was aided by a grant from the Committee for Research in Problems of Sex of the National Research Council. In the conduct of the complex investigative and statistical phases of this study, valuable services were rendered by various members of the departmental research staff, especially by Drs. G. Colom, J. Danek and K. Planansky, by Miss G. Freedman, and by Messrs. A. Falek, M. Gelfarb, W. Shaw and J. Tieman.

expected to undergo a habitual fixation without the pre-existence of the various organic components of sexuality, which may sometimes fail to be integrated into a mature form of sex behavior. The validity of this statement remains unchanged, regardless of whether its reference is to the maturational or to the adjustive specifications of homosexual behavior patterns, and regardless of whether the term "homosexuality" is applied to the formation of all, or only to the practice of overt, sexual relations between individuals of the same sex.

Organic Basis of Sex Development. Irrespective of subsequent interferences with the integration of psychosexual maturation patterns, biologically it is quite certain that the developmental potentialities of one or the other sex are originally determined by the chromosomal organization of the gametes. The differentiation of maturational processes cannot begin, unless every cell of the developing embryo and ultimate adult has been provided with the original XX- or XY-constitution of the fertilized ovum. Gonadal hormones play an important part in activating the long process of maturation. According to Stern (22), however, they are only the tools, with which the genetic constitution of an organism directs its sexual development from a morphologically neutral embryonic stage to the functional responsiveness of adult sex adjustment.

As a rule, the balance established between the sex-controlling effect of one or two X-chromosomes and that of the other chromosomes is known to operate with a sufficient margin of safety to preclude intersexual development, that is, imperfect determination of one or the other sex due to a disturbed balance of female and male genetic tendencies. However, if a breakdown in the usual process of clearly alternative differentiation between the sexes occurs, the maturational effect of one or the other of the opposing sets of sex genes may be weakened precariously. Such an organic disarrangement is likely to lead to a variety of intersexual deviations, and thereby interferes with the full integration of ordinary patterns of sexual maturation.

Psychodynamic Versus Genetic Theories of Homosexuality. According to *psychodynamic* theories of sociological or psychoanalytical orientation, a possible causal relationship between an organically disarranged sex constitution and a tendency to overt homosexuality in the adult can be safely disregarded. A certain degree of sexual feeling toward one's own sex is assumed to remain a residual trait in every person, as the result of what is originally considered to be a complete freedom of choice. Subsequent preference for predominantly homosexual patterns is believed to be a product of individual learning and experience (4, 8, 18, 19). Final adherence to homosexual outlets in men is ascribed either to the conditioning compulsiveness of social ostracism with respect to common "physiological" deviations from the moral code of our society (10, 14) or to traumatized regression and fixation to immature levels of sexuality (1, 2, 6). In line with the latter concept, inversive anxiety may be aroused by competitiveness in the oedipal situation, and is apt to result in one

of two possible patterns of response; namely, in seductive submission to the parental rival or in erotized identification with the mother.

The apparent psychodynamic significance of a more specific type of *personality deviation* has been emphasized by a group of psychiatrically trained investigators, especially by Bychowski, Hoch, and Rado (10). In their opinion, the most common form of personality change observed in homosexual men is that of a schizoid or "schizo-sexual" disorganization, distinguished by certain schizophrenia-like obsessions and a compulsive insistence upon pregenital or paragenital gratification patterns. However, this explanation depends on the concept of "early pan-sexuality" as a possible cause of male homosexuality (in the sense of a polymorphic-perverse stage of psychosexual development) and has been entirely rejected by Kinsey and other biologists (10).

Very few contemporary investigators have shown an inclination to give cautious support to a *genetic* theory of male homosexuality as originally suggested by Krafft-Ebing (16). In the opinion of Henderson and Gillespie (7), the probability of a primary constitutional basis in some apparently conditioned types of male homosexuality is indicated not only by the frequency of physical characteristics belonging to the female sex, but also by the unusual number of homosexual men displaying special artistic ability. Familial occurrence, notably in brothers, is said by Hirschfeld (9) to have been observed in 35% of homosexual males, and some attention has been given to the hypothesis of an intersexual origin of certain forms of human homosexuality, although it had been formulated on the basis of Goldschmidt's experiments conducted with gypsy moths. The main support for the application of this theory in man has come from the observation, made by Lang (17) as well as by Jensch (11), that the sex ratio among the siblings of male homosexuals seems to deviate sharply from ordinary expectation.

However, the *statistical* adequacy of these studies has been criticized severely (5, 15). Equal validity is probably attached to Kinsey's statement that an increase in the homosexuality rates for the blood relatives of homosexuals has never been substantiated by means of statistically satisfactory investigations (14). It is evident, too, that if some homosexual men are assumed to be genetically female although phenotypically male intersexes without a Y-chromosome, their children should all be female. It would be preferable, therefore, to ascertain a significant deviation of the expected sex ratio in relation to the *offspring* rather than the siblings of homosexual males. In fact, the most conclusive test of the intersexuality theory would consist in a cytological examination of chromosomal biopsy material, which should show the lack of a Y-chromosome in intersexes with a known homosexual history (21). In the absence of such cytological data, it is fair to admit that the question of the possible significance of genetic mechanisms in the development of overt homosexuality must still be regarded as entirely *unsettled*.

Organization of the Present Study. Taking notice of this generally unsatisfactory state of information about the genetic aspects of adult homosexual behavior—methodologically long recognized as one of the thorniest topics of research—, our investigative program was planned as a concentric and strategically coordinated attack from different directions (13). The frontal approach was designed to yield comparative sex records of a statistically representative sample of predominantly or exclusively homosexual twin subjects over age 20, to be collected not only from a diversified assortment of psychiatric and correctional institutions, but also through direct contacts with the clandestine homosexual world. Other thrusts were aimed at the procurement of clinical, morphological and sociological data (a) for graduated sex ratings of both male twin index cases and single-born homosexual men as well as for those of their fathers, brothers and half-brothers and (b) for a statistically verified determination of the sex ratios among the siblings and children of both groups of index cases. However, we are ready to concede at this point that some of our original objectives remained beyond reach even within the framework of our veteran research organization.

The main reason for the given tactical setbacks may be seen in the fact that in family studies of a sexually aberrant group it is very much easier to devise scientific criteria and investigative goals than it is to attain them in actual practice, that is, in direct contacts with a series of habitually distrusting research subjects who tend to live far away from their families. As an illustration of the difficulties encountered in a study of this kind, it may be mentioned only that suitable index cases are astute in disguising their identities, personal activities and family connections. Even after having been located, they remain very poor specimens for cytological work or other laboratory examinations, simply because many of them insist upon interviews to be arranged in accordance with their habits of precaution, that is, at neutral meeting places.

Fathers and Children of the Index Cases. It is also clear that sex classifications can be made only of those children of homosexual subjects, who have been born. However, the total size of this birth-rate must be expected to be inversely related to the accuracy of the criteria applied in the search for homosexual index cases. In fact, if the present analysis is limited to two comparable samples of 85 twin subjects and 112 single-born index cases with fully recorded sex and family data and with a plainly homosexual history after adolescence, our survey provides verified evidence only of a total of 11 ***marriages*** contracted by homosexual men with a Kinsey rating of group 3 or higher. Most of these marriages lasted no longer than a few months, and only three of them were fertile, resulting in a total fertility quota of five ***children,*** three boys and two girls. Unfortunately, in no instance has it been possible to confirm the paternity of the legal fathers beyond reasonable doubt.

The data on the sex histories of the ***fathers*** of the index cases are equally

disappointing. In most instances, no way could be found to reach the given persons for a personal interview or to obtain adequate information about them. It may only be stated, therefore, that of a total of 88 fathers investigated, no more than two had court records, which substantiated a history of overt homosexual activities in their adult lives.

Sex Distribution in the Sibships. The sex distribution of the *siblings* of the index cases is recorded in tables 1 and 2. These data have been arranged in such a manner that the sex ratios observed in the sibships of our single-born and twin index samples of homosexuals can be compared not only with the conflicting surveys of Lang (17) and Darke (5) conducted under completely different conditions in Germany and the United States, respectively, but also with the entirely unrelated sex data obtained in New York City for the sib-

TABLE 1. SEX DISTRIBUTION IN THE SIBSHIPS OF SINGLE-BORN MALES WITH AND WITHOUT A HISTORY OF OVERT HOMOSEXUALITY IN ADULTHOOD

			NUMBER OF PERSONS			SIBSHIP SEX RATIO (RELATED TO 100 FEMALES*)		
			Index Cases	Brothers	Sisters	Males	t	x^2
Previous Studies	German Homosexuals (Lang)	Over Age 25	499	956	745	128.3	3.92†	15.07†
		All Ages	1015	1734	1432	121.1	3.67†	13.54†
	American Prison Homosexuals (Darke)	Over Age 25	56	96	101	95.0	0.80	0.62
		All ages	100	178	168	106.0	0.04	0.00
Present Study	New York Homosexuals	Over Age 25	68	168	132	127.3	1.55	2.43
		All Ages	112	263	208	126.4	1.87	3.54
	Control Group of Institutional Employees	Over Age 25	101	161	152	105.9	0.04	0.00
		All Ages	116	185	167	110.8	0.41	0.16

* Expected Sex Ratio: 106 Males to 100 Females.
† Significant at the 1% Level of Confidence.

ships of two apparently non-homosexual control groups. One control group consists of a consecutive series of adult male twins distinguished by a history of pulmonary tuberculosis (table 2), while the other group comprises all the male employees of the Psychiatric Institute (table 1). The observed sex ratios in their sibships are 92:100 and 110:100, respectively, and are clearly within the limits of statistical expectation. According to both the t test and the chi-square, a difference as large as, or larger than, the one observed between the theoretical ratio of 106 males:100 females and the ratio 92:100 found in the sibships of tuberculous twins would actually be expected to occur by chance nearly 15 per cent of the time.

By contrast, a fairly consistent tendency to deviate toward an excess of males appears to express itself in the sibships of our single-born and twin

index samples of homosexual men. The given sibship sex ratios are 126:100 and 125:100, respectively, and seem to be in notable agreement with the ratio of 121:100 observed by Lang. However, contrary to the deviant ratio in Lang's sample, which is statistically significant at the 1 per cent level of confidence, the deviations in our numerically smaller sibship groups fail to reach statistical significance even at the 5% level of confidence and with respect to both t and chi-square values. Statistically speaking, a difference as large as, or larger than, the ones obtained between the theoretical ratio and the two ratios observed in our samples would be expected to occur by chance about 6% of the time (13).

In order to preclude the possibility of a few large and predominantly male sibships being responsible for the observed deviation in the sex ratio, the sibships of the single-born homosexual sample have been analyzed as to whether they do or do not share a particular excess of males. Taking into account the various sibship sizes, one would expect to find an excess of males in 47.6 of the 112 sibships studied. Actually, 51 sibships show such an excess. How-

TABLE 2. SEX DISTRIBUTION IN THE SIBSHIPS OF ADULT MALE TWINS WITH A HISTORY OF OVERT HOMOSEXUALITY OR PULMONARY TUBERCULOSIS

		NUMBER OF PERSONS			SIBSHIP SEX RATIO (RELATED TO 100 FEMALES)		
		Index Cases	Brothers	Sisters	Males	t	χ^2
Homosexual Twins	Over Age 25	68	85	65	130.8	1.26	1.59
	All Ages	85	104	83	125.3	1.14	1.27
Tuberculous Twins	Over Age 25	81	174	175	99.4	0.63	0.38
	All Ages	104	206	224	92.0	1.50	2.22

ever, the observed difference is smaller than the standard deviation and, therefore, may be expected by chance.

It is possible, of course, that the disproportioned sex distribution among the siblings of the two New York State samples of homosexuals is by no means accidental and discloses a lack of statistical significance only because of their limitations in size. However, no more than a suggestive trend can be assumed on the basis of the available data, and careful re-examination of this trend in more extensive samples appears necessary. Particular attention should be given in these studies to the possibility of a specific genetic mechanism modifying the control of the sex ratio, a theory advanced very recently by Bernstein (3) in order to explain the tendency of a statistically excessive number of families to produce offspring of one sex only or primarily one sex.

According to this theory, the genes controlling the sex ratio act through the endocrine system, especially the sex hormones, and may even be identical with the genes controlling the male-female sex hormone balance. It has been observed, for instance, that bald and unusually aggressive-masculine fathers

have an excess of boys, while the reverse seems to be true for the matings of fathers who are "in professions in which many famous women are engaged, i.e., actors, social workers, fiction writers, and all kinds of artists." If it is correct to assume, in view of Bernstein's findings, that X-bearing sperms (because of their female chromosomal balance) form a foreign entity in the male reproductive organs and, therefore, are destroyed in smaller or larger number inside the male (depending on the degree of maleness), it is quite obvious that the entire question as to the possible biological significance of

TABLE 3. GRADUATIONS OF OVERT HOMOSEXUALITY (KINSEY'S RATING SCALE) IN THE COTWINS OF 85 MALE HOMOSEXUALS

SEX CLASSIFICATION	TWIN INDEX CASES			ONE-EGG COTWINS						TWO-EGG COTWINS					
	Age	Zygocity		6	5	4	3	2, 1, 0	Unclassified	6, 5	4, 3	2	1	0	Unclassified*
		One-Egg	Two-Egg												
6	18–25	2	2	2	—	—	—	—	—	—	1	1	—	—	—
	26–35	10	8	8	1	—	—	—	1	—	—	—	2	1	5
	Over 35	8	9	6	2	—	—	—	—	—	—	—	3	4	2
5	18–25	3	3	—	1	—	1		1	—	—	—	—	2	1
	26–35	2	3	1	—	—	1	—	—	—	—	—	—	1	2
	Over 35	5	5	2	2	1	—	—	—	—	—	—	1	2	2
4	18–25	—	3	—	—	—	—	—	—	1	—	—	—	—	2
	26–35	2	3	—	—	2	—	—	—	—	1	—	—	1	1
	Over 35	3	3	—	1	—	2	—	—	—	—	—	—	1	2
3	18–25	2	2	—	1	—	—	—	1	—	—	—		1	1
	26–35	1	1	—	1	—	—	—	—	—	—	—	1	—	—
	Over 35	2	3	—	—	2	—	—	—	—	—	—	—	2	1
Total Number ...		40	45	19	9	5	4	0	3	1	2	1	7	15	19

* Including 14 females and 5 unclassified males (deceased or otherwise unavailable).

deviant sex ratios in different samples of family units must be carefully re-examined.

Comparative Homosexuality Ratings. In any case, more conclusive than the data on the sex distribution in the sibships of the two samples of homosexual index cases are the comparative sex ratings of their *brothers and cotwins*, if they are related to the given differences in the degree of blood relationship. The sex classifications of 40 monozygotic and 45 dizygotic twin index pairs are compared in table 3, while those of the brothers and half-brothers have been omitted because of incompleteness. Generally speaking, the homosexuality rates of the brothers and dizygotic cotwins of homosexual index cases do not seem to differ significantly. In either category, about 60% of the adult males

reveal no evidence of overt homosexual experiences after the onset of adolescence.

In the dizygotic group of index pairs, concordance as to overt homosexual behavior varies from 11.5 to 42.3%, according to whether the given rates are related to the two highest homosexuality ratings (5–6) or to the total range of Kinsey's classifications (1–6). Although these concordance rates may be acceptable only as minimum figures, they are slightly higher than Kinsey's rates of 10% and 37%, respectively, for the total male population. According to Kinsey's observations in men, distinguished by their willingness to cooperate with a study of their sexual behavior, 37% of all males admit to at least some overt homosexual experience between adolescence and old age, while 10 per cent are said to be more or less exclusively homosexual for at least three years between the ages of 16 and 55. In view of the fact that relatives of our index cases were requested only to cooperate with the investigative aims of a twin study and not with those of a sex study, it seems reasonable to conclude that the tendency to overt homosexuality in adulthood is *moderately increased* in men, who are the brothers or dizygotic cotwins of predominantly or exclusively homosexual index cases.

A completely different situation is encountered in those index pairs classified as *monozygotic*. This series of 40 pairs does not include a single cotwin of an overtly homosexual person standing at least midway on the homosexuality scale, who is classifiable either as entirely heterosexual or as homosexual below group 3. The majority of one-egg pairs not only are fully *concordant* as to the overt practice and quantitative rating of their aberrant sex pattern, but they even tend to be *very similar* in both the part taken in their individual sex activities and the visible extent of feminized appearance and behavior displayed by some of them.

It also seems significant that most of our index pairs assert to have developed their sexual tendencies *independently* and often *far apart* from each other, and that all of them deny categorically any history of *mutuality* in overt sex relations. The ostensible aversion to such an incestuous relationship is expressed even by those twin subjects who admit pre-adolescent sex play with a sister. In fact, the sexual taboo between homosexual twin brothers is generally carried so far that they disclaim not only the possibility of having had the same sex partner but also that of being familiar with any intimate details of a cotwin's sex life. Apparently, the habitual secretiveness of homosexual men is maintained even by twin brothers who live together and have formed an entity in many other respects.

Biological Theory of Overt Homosexuality. In an attempt to fit the palpable results of this study into a sufficiently broad and genetically sound concept of male homosexuality, it seems advisable to view overt homosexual behavior in the adult male as an *alternative minus variant* in the integrative process of

psychosexual maturation rather than as a pathognomonically determinative expression of a codifiable entity of behavioral immaturity. Apparently, the interactions between the biological components of sexual maturation and the adjustive phenomena of personality development form such a central and inseparable interrelationship that fractional deviations in the psychosomatic integration of the sex function from its pregenital elements to genital maturity may dislocate the axis, around which the organization of the personality takes place.

On the whole, the adaptational equilibrium between the potentialities of organic sex differentiation and the consequent patterns of psychosexual behavior seems to be so labile, that the attainment of a maturational balance may be disarranged at different developmental stages and by a variety of disturbing mechanisms. The range of such a *multiple causation* of inversive tendencies apparently extends from an unbalanced effect of opposing sex genes to the equivalent of compulsive rigidity in a schizoid personality structure. From a genetic standpoint, this range would be comparable to the extent of developmental possibilities in relation to left-handedness, which as an alternative variant in the integration of handedness is in a predominantly right-handed human world what adult homosexuality is in the sexually reproductive human species. As to left-handedness, however, very few investigators claim that a genically controlled basis or a certain unilateral use of the function of the left hand is precluded by a conditioned dexterity of the right hand, while analogous assumptions with respect to homosexual behavior are bitterly contended.

The disintegrative impact of those factors, which may lead to a psychosexual incapacity—rather than an optional dislike—for true love attachments on a mature heterosexual level, clearly expresses itself in a virtually complete degree of *concordance* as to overt male homosexuality in the present sample of *one-egg* twins. It is indicated by this finding that two males, who are very similar in the basic components of their personality organization, are much more likely than dizygotic twin brothers or ordinary siblings to be alike in those specific vulnerabilities, which favor a trend toward fixation or regression to immature levels of sexuality. The infeasibility of the old theory, which associated a narcissistic preference for a homosexual object choice with a striking physical resemblance between homosexual partners, is demonstrated by a complete *lack of mutuality* in the sex histories of homosexual twin brothers.

If the observed concordance rates for dizygotic index pairs and Kinsey's homosexuality ratings for the total male population are statistically comparable, their rather close correspondence weakens the significance of some popular etiologic concepts of male homosexuality. Apart from militating against the probability of a *special genetic factor*, capable of turning the psychosexual integration of the adult male into an overt homosexual pattern, the observation of an only moderately increased *concordance rate* of overt homosexuality

in genetically dissimilar twin brothers raised together plainly diminishes the plausability of explanations, which over-stress the importance of such precipitating or perpetuating factors as social ostracism, incompetence of a particular parent, or other potentially traumatizing experiences arising from the effect of uncontrolled imperfections in the structure of modern human societies. Of course, the general conclusion that habitual predominance of a homosexual behavior pattern results from disturbing experiences only in a *limited* number of persons, by no means minimizes the psychodynamic significance of these constellational factors in potentially vulnerable individuals.

The *intersexuality* theory or, more precisely, a genetically oriented "*imbalance*" theory is still based upon statistically insufficient and cytologically unconfirmed evidence, but it has not been eliminated as a possible explanation for certain groups of male homosexuals. The principle of a disturbed balance between male and female genetic tendencies in these cases would not even be invalidated by the observation that some homosexual men may have both a Y-chromosome and children who are boys. It is conceivable that phenotypically male homosexuals, who may be the product of an intersexual imbalance, are generally the ones distinguished by *infertility*. In view of some observed but statistically still questionable deviations in the sex ratio of affected index sibships, it is even more likely that the underlying disturbance is *hormonal* in nature, in the sense of a genically controlled disarrangement in the male-female sex hormone balance, rather than the result of a chromosomal (mutational) aberration or of an incomplete process of sex-reversal.

CONCLUSIONS

In conclusion, it may be stated that a full understanding of the biological factors, which interact in the formation of overtly homosexual behavior patterns, still requires a great deal of basic research. One may be justified to add that twin studies alone will probably not suffice to accomplish this major task, although a recognition of certain limitations of the twin study method does not seem to warrant its classification as "too crude" (20). Quite the contrary, adequately selected and statistically refined combinations of twin-sibship studies (12) with cytological, biometric and endocrinological investigations in the given family units are virtually certain to play an essential part in the further advancement of our knowledge regarding the biological components of sexual maturation and the differentiation of sexual behavior patterns.

It is also quite evident that the presently available genetic evidence, especially the observation of practically complete concordance as to overt homosexuality in monozygotic male twin pairs, throws considerable doubt upon the validity of purely psychodynamic theories of predominantly or exclusively homosexual behavior patterns in adulthood and correspondingly strengthens the hypothesis of a genically determined disarrangement in the balance between

male and female maturational (hormonal) tendencies. In any case, the need of additional work in relation to the genetic aspects of homosexuality cannot possibly be questioned. The urgency of such work is undeniable as long as this aberrant type of behavior continues to be an inexhaustible source of unhappiness, discontentment, and a distorted sense of human values.

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THIS section, prepared by Dr. V. Rae Phelps, continues the list of current research articles and books of special interest to students of human heredity, which was started with the first issue of Volume I, covering the year 1949. The present list includes publications issued in 1951 (Part 3). For further information regarding the organization of the Bibliography, see Parts 3 and 4 of the 1950 list published in Volume 3.

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